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  *      APS is unavailable Thanksgiving Day, Christmas Day,     *
  *      and New Year's Day.                                     *
  *                                                              *
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  *        U. S.   P A T E N T   T E X T   F I L E              *
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  *  THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT            *
  *  THROUGH May 25,1999.                                        *
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=> e sims, peter ?/in

E#      FILE            FREQUENCY  TERM
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E1      USPAT                1     SIMS, PAUL E/IN
E2      USPAT                2     SIMS; PEGGY L/IN
E3      USPAT                0 --> SIMS, PETER ?/IN
E4      USPAT                8     SIMS, PETER J/IN
E5      USPAT                1     SIMS, PETER JAMES/IN
E6      USPAT                3     SIMS, PETER S/IN
E7      USPAT                1     SIMS, PHILIP FRANKLIN/IN
E8      USPAT                1     SIMS, RALPH W/IN
E9      USPAT                1     SIMS, RAYMOND B/IN
E10     USPAT                6     SIMS, RAYMOND E/IN
E11     USPAT                1     SIMS, RAYMOND U/IN
E12     USPAT                1     SIMS, REX/IN

=> s e4,e5

             8 "SIMS, PETER J"/IN
             1 "SIMS, PETER JAMES"/IN
L1           9 ("SIMS, PETER J"/IN OR "SIMS, PETER JAMES"/IN)

=> d l1 1-9


1.  5,886,314, Mar. 23, 1999, Pipe cutting apparatus; Peter James
Sims, 219/121.44, 61.3, 61.5, 121.59; 266/57 [IMAGE AVAILABLE]

2.  5,843,884, Dec. 1, 1998, C9 complement inhibitor; Peter J. Sims,
514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2 [IMAGE AVAILABLE]

3.  5,763,156, Jun. 9, 1998, Inhibition of complement mediated
inflammatory response; Peter J. Sims, et al., 435/4, 2, 7.1, 7.2,
7.21, 29, 325, 366, 372, 374; 436/821; 604/7 [IMAGE AVAILABLE]

4.  5,705,732, Jan. 6, 1998, Universal donor cells; Peter J. Sims, et
al., 800/17; 536/23.1; 800/14, 18 [IMAGE AVAILABLE]

5.  5,660,825, Aug. 26, 1997, Method of inhibition of complement mediated
inflammatory response; Peter J. Sims, et al., 424/130.1, 131.1,
141.1, 158.1, 810; 514/2, 12; 530/387.2, 388.25 [IMAGE AVAILABLE]
```

6. 5,635,178, Jun. 3, 1997, Inhibition of complement mediated inflammatory respons[redacted]sing monoclonal antibodies sp[redacted]fic for a component forming th[redacted]56-9 complex which inhibit th[redacted]atelet or endothelial cell activating function of the C56-9 complex; **Peter J. Sims**, et al., 424/145.1; 530/388.25 [IMAGE AVAILABLE]

7. 5,573,940, Nov. 12, 1996, Cells expressing high levels of CD59; **Peter J. Sims**, et al., 435/362; 424/93.21; 435/69.1 [IMAGE AVAILABLE]

8. 5,550,108, Aug. 27, 1996, Inhibition of complement mediated inflammatory response; **Peter J. Sims**, et al., 514/21, 2, 8, 12; 530/350, 380, 830 [IMAGE AVAILABLE]

9. 5,135,916, Aug. 4, 1992, Inhibition of complement mediated inflammatory response; **Peter J. Sims**, et al., 514/21, 2, 8, 12; 530/350, 380, 830 [IMAGE AVAILABLE]

=> s l1 and cd59

```
            41 CD59
L2           3 L1 AND CD59
```

=> d l2 1-3

1. 5,843,884, Dec. 1, 1998, C9 complement inhibitor; **Peter J. Sims**, 514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2 [IMAGE AVAILABLE]

2. 5,705,732, Jan. 6, 1998, Universal donor cells; **Peter J. Sims**, et al., 800/17; 536/23.1; 800/14, 18 [IMAGE AVAILABLE]

3. 5,573,940, Nov. 12, 1996, Cells expressing high levels of **CD59**; **Peter J. Sims**, et al., 435/362; 424/93.21; 435/69.1 [IMAGE AVAILABLE]

=> s l2 and (cd59(P)(42 or 58)

UNMATCHED LEFT PARENTHESIS 'AND (CD59'

=> s l2 and (cd59)(P)(42 or 58)

```
            41 CD59
       1025997 42
        624178 58
             4 (CD59)(P)(42 OR 58)
L3           0 L2 AND (CD59)(P)(42 OR 58)
```

=> s l2 and (cd59)(P)(c9)

```
            41 CD59
          6937 C9
            11 (CD59)(P)(C9)
L4           3 L2 AND (CD59)(P)(C9)
```

=> d l4 1-3 date

L4: 1 of 3

TITLE:	C9 complement inhibitor		
US PAT NO:	5,843,884 [IMAGE AVAILABLE]	DATE ISSUED:	Dec. 1, 1998
APPL-NO:	08/559,492	DATE FILED:	Nov. 15, 1995

L4: 2 of 3

TITLE:	Universal donor cells		
US PAT NO:	5,705,732	DATE ISSUED:	Jan. 6, 1998

[IMAGE AVAILABLE]
APPL-NO: 08/08[redacted]07 DATE FILED: [redacted]ul. 1, 1993
REL-US-DATA: Conti[redacted]ion-in-part of Ser. No. 906,[redacted] Jun. 29, 1992, abandoned, and Ser. No. 271,562, Feb. [redacted]7, 1994, Pat. No. 5,573,940, which is a continuation-in-part of Ser. No. 729,926, Jul. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.

L4: 3 of 3

TITLE: Cells expressing high levels of **CD59**
US PAT NO: 5,573,940 DATE ISSUED: Nov. 12, 1996
[IMAGE AVAILABLE]
APPL-NO: 08/271,562 DATE FILED: Jul. 7, 1994
REL-US-DATA: Continuation of Ser. No. 729,926, Jul. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 365,199, Jun. 12, 1989, Pat. No. 5,135,916.

=> d l4 1-3 kwiuc

'KWIUC' IS NOT A VALID FORMAT FOR FILE 'USPAT'
ENTER DISPLAY FORMAT (CIT):kwic

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L4: 1 of 3
INVENTOR: **Peter J. Sims**, Mequon, WI

ABSTRACT:
Pharmaceutical compositions are designed based on the criticality of a portion of **C9** for assembly of the C5b9 complex, which specifically modulate binding of **CD59** to **C9**, either molecules structurally mimicking **C9** amino acid residues 359 to 384 which bind to **CD59** or molecules binding to **C9** amino acid residues 359 to 384. Molecules which inhibit **CD59** binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic antibodies immunoreactive with **C9** amino acid residues 359 to 384. Molecules which prevent assembly of the C5b-9 complex include antibodies and antibody fragments immunoreactive with amino acid residues 359 to 384 of **C9**, peptides that bind to amino acid residues 359 to 384 of **C9**, and nucleotide molecules that bind to amino acid residues 359 to 384 of **C9**.

SUMMARY:

BSUM(8)

There . . . are normally protected from these effects of complement by cell-surface proteins that specifically inhibit activation of the C5b-9 pore upon **C9** binding to membrane C5b-8, as reported by Holguin, M. H., et al., J. Clin. Invest. 84, 7-17 (1989); Sims, P.. . . Acad. Sci., U.S.A. 83, 6975-6979 (1986) and Schonermark, S., et al., J. Immunol. 136, 1772-1776 (1986), and the leukocyte antigen **CD59**, described by Sugita, Y., et al., J. Biochem. (Tokyo) 104, 633-637 (1988); Holguin, M. H., et al., (1989); Sims, P.. . . et al., (1990). Accumulated evidence suggest that these two proteins exhibit quite similar properties, including the following: both HRF and **CD59** are tethered to the cell surface by a glycolipid anchor, and are deleted from the membranes of the most hemolytically. . . in the stem cell disorder paroxysmal nocturnal hemoglobinuria; the activity of both inhibitors is species-restricted, showing selectivity for C8 and **C9** that are derived from homologous (i.e. human) serum; and both HRF and **CD59** appear to function by inhibiting the activation of **C9** , decreasing the incorporation of **C9** into the membrane C5b-9 complex, and limiting propagation of the **C9** homopolymer.

SUMMARY:

BSUM(9)

In . . . thereof relating to polypeptides having the ability to act as an inhibitor of complement C5b-9 complex activity. The compositions contain **CD59**, active derivatives or fragments thereof which act to inhibit the activity of C5b-9, anti-idiotypic antibodies mimicking the action of the inhibitor proteins or antibodies against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to inhibit C5b-9 related stimulatory. . .

SUMMARY:

BSUM(10)

Human (hu).sup.1 **CD59** antigen is a 18-21 kDa plasma membrane protein

that functions as an inhibitor of the C5b-9 membrane attack complex (MAC) of hu complement. **CD** interacts with both the C8 and components of MAC du g its assembly at the cell su e, thereby inhibiting formation of the membrane-inserted **C9** homopolymer responsible for MAC cytolytic activity. This serves to protect hu blood and vascular cells from injury arising through activation of complement in plasma. **CD59**'s inhibitory activity is dependent upon the species of origin of C8 and **C9**, with greatest inhibitory activity observed when **C9** is from hu or other primates. By contrast, **CD59** exerts little or no inhibitory activity towards C8 or **C9** of most other species, including rabbit (rb). Because the activity of **CD59** is largely restricted to regulating hu **C9**, and the activity of analogous complement inhibitors expressed by cells of other species is likewise generally selective for homologous **C9**, xenotypic cells and tissue are particularly susceptible to complement-mediated destruction due to unregulated activity of MAC. This phenomenon underlies hyperacute. . .

SUMMARY:

BSUM(11)

Analysis of the physical association of **CD59** with components of MAC suggested that separate binding sites for **cD59** are contained within the .alpha.-chain of hu C8 and within hu **C9**. Within **C9**, this site(s) has been mapped to between residues 334-415. The complement-inhibitory activity of **CD59** is species-selective, and is most effective towards **C9** derived from human or other primate plasma. The species-selective activity of **CD59** was recently used to map the segment of human **C9** that is recognized by this MAC inhibitor, using recombinant rabbit/human **C9** chimeras that retain lytic function within the MAC [Husler T, Lockert D. H., Kaufman K. M., Sodetz J. M., Sims P. J. (1995). J. Biol. Chem. 270:3483-3486]. These experiments suggested that the **CD59** recognition domain was contained between residues 334-415 in human **C9**.

SUMMARY:

BSUM(16)

CD59 interacts with a segment of human **C9** (hu **C9**) between residues 334-415, immediately C-terminal to the predicted membrane-inserting domain of **C9**. This segment of **C9** contains a region of markedly divergent sequence when hu **C9** is compared to **C9** of other species, with greatest divergence noted for the peptide segment contained within an internal Cys359-Cys384 disulfide in hu **C9**. In order to determine whether sequence contained in this peptide loop represents a hu **C9**-specific motif that is selectively recognized by **CD59**, **CD59**'s inhibitory activity toward various full-length **C9** chimeras containing hu-unique or rabbit (rb)-unique sequence spanning this segment of the **C9** polypeptide were analyzed. These experiments revealed that substitution of hu residues 359-391 into otherwise rb **C9** yielded a chimera indistinguishable from hu **C9** in its regulation by **CD59**. **C9** chimeras generated by substitution of hu **C9** sequence flanking either side of residues 359-391 into rb **C9** showed no consistent increase in inhibition by **CD59**. This indicates that only residues contained between 359-391 of hu **C9** are directly recognized by **CD59**. Moreover, truncation of the segment of hu **C9** sequence in chimeric rb **C9** from 359-391 to the putative recognition loop of hu 359-384 was accompanied by approximately 35% reduction of **CD59** inhibitory function. Further, **CD59** specifically bound to a synthetic peptide corresponding to residues 359-384 of hu **C9**. IgG (Fab) specific for the hu **C9** 359-384 peptide inhibited the hemolytic activity of hu **C9** (but not rb **C9**) in a manner analogous to **CD59**.

SUMMARY:

BSUM(17)

Pharmaceutical compositions are designed based on the criticality of this portion of **C9** for assembly of the C5b9 complex which specifically modulate binding of **CD59** to **C9**, either molecules structurally mimicking **C9** amino acid residues 359 to 384 which bind to **CD59** or molecules binding to **C9** amino acid residues 359 to 384. Molecules which inhibit **CD59** binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic antibodies immunoreactive with **C9** amino acid residues 359 to 384. Molecules which prevent assembly of the C5b-9 complex include antibodies and antibody fragments immunoreactive with amino acid residues 359 to 384 of **C9**, peptides that bind to amino acid residues 359 to 384 of **C9**, and nucleotide molecules that bind to amino acid residues 359 to 384 of **C9**.

DRAWING DESC:

DRWD(2)

FIGS. 1A and 1B are a plot of the inhibitory activity of **CD59** towards hu/rb chimeras of complement **C9**. Bar graph (FIG. 1A) summarizes combined results of all experiments measuring the inhibitory activity of **CD59** towards recombinant hu/rb chimeras of **C9**. In each assay, hemolytic titrations of **C9** were performed against C5b-8 chE in the presence and absence of membrane **CD59**, and the percent reduction of hemolysis due to **CD59** (ordinate)was determined, with normalization to that observed for hu **C9** (100% inhibition). Error bars denote mean +S.D., parentheses indicate number of independent experiments; asterisks (*) indicate significance ($p<0.01$) when compared to rb **C9**; pound signs (#) indicate significance ($p<0.01$) when compared to hu **C9**. The protein assayed is depicted (FIG. 1B) so as to designate those portions of the polypeptide containing hu **C9** (open) or rb **C9** (shaded) sequence. Numbers above each construct indicate the junctional hu **C9** residue at each transition between hu and rb protein sequence. Bars designated as human **C9** and rabbit **C9** denote recombinantly-expressed hu and rb **C9**, respectively. Recombinant **C9** chimeras (designated as #1-12) contain human (H) or rabbit (R) sequence according to the deduced mature primary structure of hu and rb **C9**. In some **C9** chimeras, the numbering appears discontinuous because of gaps in the alignment of the hu and rb sequences: 1, R1-338H334-415R425-536; 2,. . .

DRAWING DESC:

DRWD(3)

FIG. 2 is a schematic representation of the segment of hu **C9** identified as containing the **CD59** binding site, which according to the proposed domain structure includes: thrombospondin type 1 (TS), LDL-receptor (LDLR), hinge (Hinge), membrane binding (MB), and epidermal growth factor precursor (EGFP) domains. Shaded segment indicates residues 334-415 of hu **C9**, spanning the putative **CD59** binding site. The amino acid sequence of this peptide segment Sequence ID No. 3 is given below, and is shown in an alignment with rb **C9** Sequence ID No. 4 (alignment done for full-length polypeptides with the PALIGN program in PCGENE). Asterisks indicate sequence identity. Dotted lines indicate the Cys 359/384 disulfide of hu **C9** and the assumed corresponding internal disulfide in rb **C9**. Residue numbers refer to the mature proteins.

DRAWING DESC:

DRWD(4)

FIG. 3 is a graph showing inhibitory activity of **CD59** unaffected by disruption of the 359/384 disulfide. Recombinant hu **C9** was expressed with a Cys.fwdarw.Ala mutation at either residue 384 or at both residues 359/384, and analyzed as described in FIG. 1. Inhibitory activity of **CD59** towards the hemolytic function of each recombinant **C9** is expressed as a percentage, relative to that measure for wild-type hu **C9** (ordinate). Error bars denote mean +S.D., n, indicates number of independent experiments; asterisks indicate significance (p,0.001) compared to hu **C9**. Hu **C9** and rb **C9** denote the wild type hu and rb proteins, respectively.

DRAWING DESC:

DRWD(5)

FIG. 4 is a graph showing **CD59** specifically binds hu **C9** peptide 359-384. Microplates were coated with hu **C9** peptide 359-384 coupled to BSA, and specific binding of biotin-**CD59** determined in the presence of affinity-purified antibody against hu **C9** residues 359-384 (.circle-solid.), or non-immune IgG (.DELTA.) (IgG concentrations indicated on abscissa). All data were corrected for nonspecific binding of **CD59**, determined in presence of 20-fold excess of unlabeled **CD59**. Ordinate denotes absorbance at 405 nm, with correction for nonspecific background. Error bars denote mean +S.D. Data of a single. . .

DRAWING DESC:

DRWD(6)

FIGS. 5A, 5B, 5C and 5D are graphs showing the inhibition of **C9** -dependent lysis by antibody against **C9**-peptide 359-384. Fab of antibody against hu **C9** peptide 359-384 (,circle-solid.) was tested for its capacity to inhibit the hemolytic activity of recombinant hu **C9** (Figure 5A), hu/rb **C9** chimera #7 (FIG. 5B), recombinant rb **C9** (FIG. 5C), or hu/rb **C9** chimera #12 (FIG. 5D). Residues of human (H) and rabbit (R) sequence in each **C9** chimera are indicated in FIG. 1. Also shown is data for non-immune antibody (.DELTA.) (final concentrations indicated on abscissa). In all experiments, C5b-8 chE lacking **CD59** served as target cells and hemolysis measured with correction for nonspecific lysis. Data of single experiment, representative of three similar. . .

DETDESC:

DETD(2)
I. **C9** Peptide/**CD59** **C9** binding site Immunomodulators

DETDESC:

DETD(3)

Peptide sequence in human complement protein **C9** has been identified that contributes to the recognition of this protein by its naturally occurring inhibitor, **CD59** . **CD59** is known to bind to neo-epitopes that become exposed in complement C8 and **C9** during assembly of the cytolytic membrane attack complex of proteins C5b through **C9**. Through this interaction, **CD59** interrupts assembly of the C5b-9 complex, protecting the target cell from destruction by these complement proteins. Data demonstrates that antibody raised against this human **C9**-derived peptide sequence is functionally inhibitory towards the lytic activity of the human C5b-9 complex. This permits design of reagents directed specifically at human **C9** that mimic or inhibit the complement-inhibitory function of cell-surface **CD59**.

DETDESC:

DETD(4)

Compounds which bind **CD59**

DETDESC:

DETD(5)

As demonstrated by the following example, amino acid residues 359-384 of **C9** are critical for binding of **CD59** to **C9**, resulting in inhibition of C5b-9 complex assembly. Peptides can be as short as 26 amino acids, less than forty amino acids, or less than 56 amino acids (359 to 415 amino acid peptide fragment of **C9**). Substitutions based on conserved sequence (rabbit for human, amino acids with similar structure and charge), presence or absence of a. . . elongation of the peptide through addition of supplemental amino acid sequence, were all shown not to significantly inhibit binding of **CD59** to **C9**. Other derivatives that should also be active include covalently-cyclized derivatives, for example, disulfide-bonded and amide bonded peptides.

DETDESC:

DETD(6)

The data indicates that **CD59** inhibits **C9** through binding to hu-specific residues contained within the Cys359-Cys384 disulfide loop of the polypeptide. Optimal interaction of **CD59** with this binding site in hu **C9** appears to depend upon a few residues located immediately C-terminal to this segment of the protein. Although the specific role of this segment of **C9** in membrane attack complex (MAC) assembly is unknown, the data indicates that ligand binding to this site abrogates the lytic activity of the C5b-9 complex, implicating these residues in the conversion of **C9** from solution monomer to membrane-embedded polymer. **CD59** specifically binds a human **C9**-derived peptide corresponding to residues 359-384, and antibody (Fab) raised against this **C9**-derived peptide inhibits the lytic activity of human MAC. Mutant human **C9** in which Ala was substituted for Cys 359-384 was found to express normal lytic activity and to be fully inhibited by **CD59**. This suggests that the intrachain Cys359/Cys384 disulfide bond within **C9** is not required to maintain the conformation of this segment of **C9** for interaction with **CD59**. Other substitutions can also be made without decreasing activity.

DETDESC:

DETD(7)

These compounds are effective as competitive inhibitors of **CD59**. Other compounds besides the peptides that can be used include anti-idiotypic antibodies and antibody fragments which bind to **CD59**, nucleotide molecules, and organic molecules that bind to the site on **CD59** which binds amino acids 359-384 or 359 to 391. These can be identified using screening and computer assisted design, as. . .

DETDESC:

DETD(17)

Nucleotide molecules which bind either **CD59** or the **C9** peptide can be generated in vitro, and then inserted into cells. Oligonucleotides can be synthesized on an automated synthesizer (e.g.,. . .

DETDESC:

DETD(39)

The . . . described above is that which achieves the desired effect: either to inhibit assembly of the C5b-9 complex by binding to **C9** or to bind to the endogenous **CD59** to prevent the **CD59** from inhibiting assembly of the C5b-9 complex, thereby increasing complement mediated activation of cells.

DETDESC:

DETD(40)

Inhibition of **CD59** is useful as an adjuvant for tumor therapy and as a contraceptive since its been demonstrated that ~~CD59 protects sperm from rejection~~ by antibody and complement in the female genital tract and that **CD59** expressed on human tumor cells protect those cells from complement mediated lysis.

DETDESC:

DETD(44)
Demonstration of role of a disulfide bonded peptide loop within hu **C9** in the species-selectivity of **CD59**

DETDESC:

DETD(47)

Hu complement proteins C5b6, C7, C8, and **C9**, and hu erythrocyte membrane glycoprotein **CD59** were purified and assayed as described by Davies, et al. Immunol. Res. 12, 258-275 (1993), Wiedmer and Sims, J. Membr. Biol. 84, 249-258 (1985), and Wiedmer and Sims, J. Biol. Chem. 260, 8014-8019 (1985). Hu **C9** peptide 359-384 ([allyl-K]-CLGYHLDVSLAFSEISVGAEFNKDD-[allyl-C), BSA-conjugated hu **C9** peptide 359-384, and affinity-purified rb IgG against hu **C9** peptide 359-384 were custom ordered from Quality Controlled Biochemicals (Hopkinton, Mass.). Full-length cDNA for hu **C9** was a generous gift from Dr. J. Tschopp (University of Lausanne, Epalinges, Switzerland) and is described by Dupuis, et al., Mol. Immunol. 30, 95-100 (1993), the teachings of which are incorporated herein. Full length cDNA for rb **C9** was isolated and cloned into pSVL as reported by Husler, et al., J. Biol. Chem. 270, 3483-3486 (1995), the teachings. . .

DETDESC:

DETD(58)
Biotin-**CD59**

DETDESC:

DETD(59)

CD59 was biotinylated by incubation (1 h, room temperature) with a 20-fold molar excess of NHS-LC-biotin in 10 mM MOPS, 0.1%. . .

DETDESC:

DETD(61)

Hemolytic activity of each **C9** construct was assayed using as target cells chE that were reconstituted with purified hu **CD59**, as described by Husler, et al., (1995). chE were washed extensively and suspended in GVBS, and the membrane C5b67 complex. . . C5b67 chE were diluted to

1.4.times.10.sup.8 /ml in GVBE and incubated (10 min. 37.degree. C.) with 0 or 750 ng/ml **CD59**. I ch case, the final concentrat[redacted] of Nonidet P-40 was less than 0.0 v/v). After washing in ice-c[redacted]GVBE, 2.8.times.10.sup.8 of. . . incubated (37.degree. C.) in a total volume of 100 .mu.l with 1 ng rb C8 plus 0-50 ng of recombinant **C9**, serially diluted in Opti-MEM I. Hemolysis was determined after 30 minutes at 37.degree. C., with correction for nonspecific lysis, determined in the absence of **C9**. In each experiment, the inhibitory activity of **CD59** towards each recombinant **C9** construct was determined from the reduction in complement lysis of those cells reconstituted with **CD59**, versus the identically-treated cells omitting **CD59**, measured at the midpoint of the **C9** titration (i.e., 50% hemolysis). In order to directly compare results obtained in experiments performed on different days, data for each recombinant **C9** construct were normalized to results obtained in each experiment with hu **C9**.

DETDESC:

DETD(62)
CD59 binding to hu **C9** peptide 359-384.

DETDESC:

DETD(63)

The specific binding of **CD59** to hu **C9**-derived peptide 359-384 was measured by microtiter plate assay with biotin-**CD59**, according to modification of published methods of Chang, et al. (1994) and Husler, et al. (1995). Briefly, the BSA-peptide conjugate. . . 8.5. After blocking with 1% (w/v) BSA, wells were washed and incubated (4 hrs., 37.degree. C.) with 0.5-1 , .mu.g/ml biotin-**CD59**. After washing, the bound biotin-**CD59** was detected with Vectsstain.TM. (Vector Labs, Burlingame, Calif.), developed by addition of p-nitrophenyl phosphate (2 mg/ml) and optical density recorded at 405 nm (VMAXMICROPLATE.TM. Reader, Molecular Devices, Inc.). In all experiments, correction was made for background adsorption of biotin-**CD59** to BSA-coated wells (no peptide) and for nonspecific binding of biotin-**CD59** to peptide, determined in the presence of a 20-fold excess of unlabeled **CD59**. As a positive control for specific binding, comparison was made in each experiment to wells coated with 2 .mu.g/ml hu **C9**. The capacity of monospecific antibody against hu **C9** peptide 359-384 to compete specific binding of **CD59** was determined by prior incubation of the BSA-peptide-coated wells with antibody (2 hrs., 0-100 .mu.g/ml LgG) before addition of biotin-**CD59**.

DETDESC:

DETD(65)

The capacity of antibody against hu **C9** peptide 359-384 to inhibit MAC was determined by hemolytic assay, using the chE target cells described above, omitting **CD59**. In these experiments, 0-1 mg/ml Fab of antibody against hu **C9** peptide 359-384 (or, non-immune antibody control) was added with recombinant **C9** (hu, rb, or chimeric), and complement-specific lysis determined.

DETDESC:

DETD(67)

C9 chimeras were constructed in which the segment of **C9** corresponding to the putative **CD59** binding site (residues 334-415 in hu **C9**; were interchanged between hu and rb **C9**. These chimeric proteins were then tested for hemolytic activity and for their sensitivity to inhibition by membrane **CD59** (FIG. 1A and 1B).

Substitution of hu **C9** residues 334-415 into rb **C9** (chimera #1) resulted in a protein was indistinguishable from h[redacted]9 in its sensitivity to inhibit by **CD59**. Conversely, when th[redacted]ame segment of hu **C9** was replaced by the corresponding rb **C9** sequence (chimera #8), the resulting chimera was indistinguishable from rb **C9** and virtually unaffected by the presence of membrane **CD59**. In these experiments, MAC was assembled using hu C5b67 and rb C8 so as to circumvent known inhibitory interaction of **CD59** with hu C8 (Rollins, et al. J. Immunol. 146, 2345-2351 (1991), Ninomiya and Sims J. Biol. Chem. 267, 13675-13680 (1992).

DETDESC:

DETD(68)

~~As depicted in FIG. 2, the segment of hu C9 shown to bind CD59~~ is immediately C-terminal to the putative membrane-spanning domain of the protein, and corresponds to a segment of polypeptide exhibiting particularly low sequence conversation when hu **C9** is aligned to **C9** of rb or other non-primate species. The most prominent divergence of sequence occurs between two cysteines (Cys359-Cys384 in hu **C9**) that are conserved in the hu and rb proteins. In hu **C9**, these cysteines have been shown to form an intrachain disulfide bond (below), as reported by Schaller, et al. J. Protein. . .

DETDESC:

DETD(69)

In order to further localize the segment of hu **C9** recognized by **CD59** and to determine the specific contribution of residues spanning the Cys359/384 disulfide, a series of hu/rb **C9** chimeras was constructed by interchanging segments of corresponding hu and rb **C9** sequences internal to residues 334-415 . Each of these chimeric proteins was expressed and analyzed for MAC hemolytic function, and for sensitivity to inhibition by membrane **CD59**. All resulting hu/rb **C9** chimeras were functionally active as determined by hemolytic titration against chE containing membrane C5b-8. As shown in FIG. 1, analysis of **CD59**-inhibitory activity towards each of these proteins revealed inhibition of MAC lytic activity by **CD59** was unaffected by replacement of all residues N-terminal to Cys359 of hu **C9** with corresponding rb sequence (chimera #2), whereas replacement of all residues C-terminal to residue 358 of hu **C9** with corresponding rb sequence (chimera #3) resulted in a protein indistinguishable from rb **C9** and only weakly inhibited by **CD59**. Consistent with the results for chimeras #1-3, substitution of hu **C9** residues 359-415 into the corresponding segment of otherwise rb **C9** (chimera #4) resulted in a protein that was indistinguishable from hu **C9**, suggesting that this polypeptide segment of hu **C9** (residues 359-415) contains the binding site for **CD59**.

DETDESC:

DETD(70)

To further resolve the segment of hu **C9** required for species-selective interaction with **CD59**, additional chimeras were constructed further truncating the segment of hu sequence substituted into rb **C9** (chimera #5-7). Data for these chimeras revealed that whereas hu residues 359-391 conferred full recognition by **CD59** (chimera #5), hu **C9** residues 392-415 failed to confer any recognition by **CD59** (chimera #5), hu **C9** residues 392-415 failed to confer any recognition by **CD59** when inserted into an otherwise rb **C9** (chimera #6). Truncation of the inserted segment of hu **C9** sequence from 359-391 (chimera #5) to 359-384 (chimera #7) was accompanied by a

small but significant reduction in inhibition of MAC lytic activity by **CD59**. These results im[redacted] that **CD59** directly interacts [redacted]h the segment of hu **C9** conta[redacted]d between residues 359-391, w[redacted] the peptide segment spanning the intrachain Cys359/384 disulfide substantially contributing to this interaction.

DETDESC:

DETD(71)

CD59's interaction with hu **C9** was abrogated by replacement of sequence spanning this putative **CD59** recognition domain with corresponding rb sequence (chimeras #8-12). Replacement of hu **C9** residues 334-415 with corresponding rb sequence (chimera #8) completely eliminated hu-selective interaction with **CD59**, as anticipated for results obtained for the complementary construct, chimera #1. Nevertheless, when the segment of rb-derived sequence substituted into otherwise hu **C9** was further truncated, the resulting chimeras (chimeras #9-12) retained a surprising degree of sensitivity to the inhibitory effects of **CD59**, characteristic of hu **C9**. Thus substitution of rb sequence for the residues internal to Cys359-384 of hu **C9** (chimera #12) did not significantly diminish **CD59**'s capacity to inhibit the lytic activity of **C9**, while C-terminal extension of the segment of rb sequence to residue 415 (chimera #9) did not completely eliminate interaction with **CD59**. Taken together with results for chimeras #1-5, these data indicate that whereas hu **C9** residues 359-391 alone are sufficient to confer recognition by **CD59**, segments of the polypeptide immediately flanking this segment significantly contribute to the extent to which this binding site is expressed.

DETDESC:

DETD(72)

The Cys359/384 disulfide in hu **C9** has recently been reported to be highly labile and subject to spontaneous reduction in the native protein, as reported Hatanaka,. . . Mol. Enzymol. 1209, 117-122 (1994). Since the data suggested that residues internal to Cys359/384 contribute in-large-part to species-selective recognition by **CD59**, the extent to which the **CD59** recognition site in **C9** is affected by disruption of this bond was examined. Mutant hu **C9** was expressed with Ala substitutions at Cys359 and Cys384 and tested for hemolytic activity and for sensitivity to inhibition by **CD59**. As revealed by data of FIG. 3, disruption of this disulfide bond did not significantly affect the hemolytic activity of the protein nor the capacity of **CD59** to specifically inhibit **C9** lytic activity. This suggests that the segment of hu **C9** forming the **CD59** binding site is either conformationally constrained independent of the Cys359-384 disulfide, or, that this binding site is expressed in the primary structure of hu **C9**, independent of protein folding.

DETDESC:

DETD(73)

In order to confirm that the peptide segment spanning hu **C9** 359-384 can itself mediate interaction with **CD59**, this 26 residue peptide was synthesized, coupled to BSA, and analyzed for **CD59** binding, using biotin-**CD59** conjugate in a micro plate assay. As demonstrated by FIG. 4, biotin-**CD59** specifically bound to **C9** peptide 359-384, inhibited binding was inhibited by excess unlabeled **CD59** or by antibody directed against the peptide.

DETDESC:

DETD(74)

CD59 is known to bind **C9** after **C9** incorporates int e C5b-9 complex, and through this interaction inhibit propagation of membrane-inserted **C9** polymer, limiting lytic activity of MAC. In order to confirm the importance of the peptide segment recognized by **CD59** to MAC assembly, Fab of antibody raised against the hu **C9** peptide 359-384 was tested for its capacity to inhibit the hemolytic activity of the hu C5b-9 complex, under the same condition used to evaluate the inhibitory function of **CD59**. As shown by the data of FIGS. 5 A-D, this Fab inhibited hemolytic activity of hu **C9** (FIG. 5A) and **C9** chimera #7 (representing rb **C9** containing hu **C9** residues 359-384, FIG. 1, FIG. 5B), but had no effect on the hemolytic activity of either rb **C9** (FIG. 5C) or chimera #12 (representing substitution of the corresponding segment of rb **C9** residues into hu **C9**; FIG. 1, FIG. 5D).

DETDESC:

DETD(75)

The experiments show that hu **C9** residues 359-391 promote **CD59** binding, and that this segment of hu **C9** contributes to the species-selective regulation of MAC function, providing an initial clue to the structural motif(s) through which this inhibitor selectively regulates the lytic activity of hu C5b-9 complex. These data further indicate that the capacity of **CD59** to optimally interact with this segment of hu **C9** is significantly influenced by residues immediately C-terminal to this segment of the **C9** polypeptide.

DETDESC:

DETD(76)

Whereas the data establish that residues internal to Cys359-Cys384 contribute to recognition by **CD59**, the disulfide bond between these two Cys is apparently not required either for maintenance of **C9**'s hemolytic activity within MAC, or, for normal regulation of that activity by membrane **CD59**. These conclusions derived by Cys/Ala mutagenesis in recombinant hu **C9** (FIG. 3) are consistent with previous reports indicating: (i) the intrinsic liability of the Cys 359-384 disulfide in **C9** purified from hu plasma, where spontaneous reduction of this bond did not appear to alter **C9** hemolytic activity, and (ii) that a specific **CD59** binding site is retained in reduced and carboxymethylated hu **C9**, in hu **C9**-derived peptide fragments, and can be demonstrated for E. coli fusion proteins contains hu **C9**-derived sequence spanning residues 359-384. This suggests that the **CD59** binding site expressed by this segment of hu **C9** reflects interactions between amino acid side chains that do not require formation of the Cys 359/Cys384 disulfide bond.

DETDESC:

DETD(77)

As noted above, chimeras generated by substituting limited segments of hu **C9** into rb **C9** revealed that the segment of hu **C9** between 359-384 uniquely conferred recognition by **CD59**, and that this interaction was enhanced by C-terminal extension of hu sequence to residue 391 (cf. Chimeras #1-7; FIG. 1). Surprisingly, chimeras generated by replacing these same segments of hu **C9** with corresponding rb **C9** sequence did not exhibit a complementary decrease in interaction with **CD59**, except when the segment of rb-derived sequence replaced in hu **C9** residues spanning 334-415 (cf. Chimeras #8-12; FIG. 1).

CLAIMS:

CLMS(1)

I claim:

1. A composition comprising molecules specifically modulating binding of **CD59** to **C9** selected from the group of molecules consisting of peptides of between 26 and 30 amino acids which bind to **CD59** and molecules binding to **C9** amino acid residues 359 to 384 (amino acid residues 381-406 of SEQ. ID NO. 5).

US PAT NO: 5,705,732 [IMAGE AVAILABLE] L4: 2 of 3
INVENTOR: **Peter J. Sims**, Mequon, WI
Alfred L.M. Bothwell, Guilford, CT
Eileen A. Elliot, New Haven, CT
Richard A. Flavell, Killingworth, CT
Joseph Madri, North Branford, CT
Scott Rollins, Monroe, CT
Leonard Bell, Woodbridge, CT
Stephen Squinto, Irvington, NY

SUMMARY:

=> s c9(P)(antibod?)(P)(359 or 384)

```
          6937 C9
         34972 ANTIBOD?
         11918 359
         22504 384
L6           1 C9(P)(ANTIBOD?)(P)(359 OR 384)
```

=> d l6 1 date

L6: 1 of 1

TITLE:	C9 complement inhibitor		
US PAT NO:	5,843,884 [IMAGE AVAILABLE]	DATE ISSUED:	Dec. 1, 1998
APPL-NO:	08/559,492	DATE FILED:	Nov. 15, 1995

=> d l6 1 kwic

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L6: 1 of 1

ABSTRACT:
Pharmaceutical compositions are designed based on the criticality of a portion of **C9** for assembly of the C5b9 complex, which specifically modulate binding of CD59 to **C9**, either molecules structurally mimicking **C9** amino acid residues **359** to **384** which bind to CD59 or molecules binding to **C9** amino acid residues **359** to **384**. Molecules which inhibit CD59 binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic **antibodies** immunoreactive with **C9** amino acid residues **359** to **384**. Molecules which prevent assembly of the C5b-9 complex include **antibodies** and **antibody** fragments immunoreactive with amino acid residues **359** to **384** of **C9**, peptides that bind to amino acid residues **359** to **384** of **C9**, and nucleotide molecules that bind to amino acid residues **359** to **384** of **C9**.

SUMMARY:

BSUM(17)

Pharmaceutical compositions are designed based on the criticality of this portion of **C9** for assembly of the C5b9 complex which specifically modulate binding of CD59 to **C9**, either molecules structurally mimicking **C9** amino acid residues **359** to **384** which bind to CD59 or molecules binding to **C9** amino acid residues **359** to **384**. Molecules which inhibit CD59 binding include peptides containing residues 359-384 which compete for binding with the other components of the C5b9 complex and anti-idiotypic **antibodies** immunoreactive with **C9** amino acid residues **359** to **384**. Molecules which prevent assembly of the C5b-9 complex include **antibodies** and **antibody** fragments immunoreactive with amino acid residues **359** to **384** of **C9**, peptides that bind to amino acid residues **359** to **384** of **C9**, and nucleotide molecules that bind to amino acid residues **359** to **384** of **C9**.

DETDESC:

DETD(9)

Data demonstrates that **antibody** raised against this human **C9**-derived peptide sequence is functionally inhibitory towards the lytic activity of the human C5b-9 complex. Other compounds besides **antibodies** and **antibody** fragments which also bind to this peptide portion of **C9**, thereby preventing assembly of the C5b-9 complex, include peptides, nucleotide molecules, and organic molecules that bind to amino acids 359-384 or **359** to 391. These can be identified using screening and computer assisted design, as described below.

CLAIMS:

CLMS(2)

---

2. . . . comprising molecules selected from the group of molecules consisting of peptides of between 26 and 30 amino acids comprising hu **C9** amino acid residues **359** to **384** (amino acid residues 381-406 of SEQ. ID NO. 5), anti-idiotypic **antibodies** immunoreactive with **C9** amino acid residues **359** to **384** (amino acid residues 381-406 of SEQ. ID NO. 5), and covalently cyclized peptides comprising hu **C9** amino acid residues **359** to **384** (amino acid residues 381-406 of SEQ. ID NO. 5).

=> d l6 1 fro

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L6: 1 of 1
DATE ISSUED: Dec. 1, 1998
TITLE: C9 complement inhibitor
INVENTOR: Peter J. Sims, Mequon, WI
ASSIGNEE: Oklahoma Medical Research Foundation, Oklahoma City, OK (U.S. corp.)
APPL-NO: 08/559,492
DATE FILED: Nov. 15, 1995
INT-CL: [6] A01N 1/00; A61K 38/00; A61K 39/395; C07K 16/00
US-CL-ISSUED: 514/2; 530/324, 387.1, 387.2; 424/131.1, 138.1
US-CL-CURRENT: 514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2
SEARCH-FLD: 424/138.1, 131.1; 536/23.1; 530/300, 350, 324, 387.1, 387.2; 514/2

REF-CITED:

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antibod?)(P)(inhibit? or suppress? or antagoni?)

          6937 C9
         34972 ANTIBOD?
        272628 INHIBIT?
        132382 SUPPRESS?
         21795 ANTAGONI?
L7         125 (C9)(P)(ANTIBOD?)(P)(INHIBIT? OR SUPPRESS? OR ANTAGONI?)
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```
=> s l7(P)(cd59)

            41 CD59
L8           3 L7(P)(CD59)

=> d l8 1-3 date

                                                          L8: 1 of 3
TITLE:          C9 complement inhibitor
US PAT NO:      5,843,884                 DATE ISSUED:    Dec. 1, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/559,492                DATE FILED:     Nov. 15, 1995

                                                          L8: 2 of 3
TITLE:          Universal donor cells
US PAT NO:      5,705,732                 DATE ISSUED:    Jan. 6, 1998
                [IMAGE AVAILABLE]
APPL-NO:        08/087,007                DATE FILED:     Jul. 1, 1993
REL-US-DATA:    Continuation-in-part of Ser. No. 906,394, Jun. 29, 1992,
                  abandoned, and Ser. No. 271,562, Feb. 7, 1994, Pat. No.
                  5,573,940, which is a continuation-in-part of Ser. No.
                  729,926, Jul. 15, 1991, abandoned, which is a
                  continuation-in-part of Ser. No. 365,199, Jun. 12, 1989,
                  Pat. No. 5,135,916.

                                                          L8: 3 of 3
TITLE:          Cells expressing high levels of CD59
US PAT NO:      5,573,940                 DATE ISSUED:    Nov. 12, 1996
                [IMAGE AVAILABLE]
APPL-NO:        08/271,562                DATE FILED:     Jul. 7, 1994
REL-US-DATA:    Continuation of Ser. No. 729,926, Jul. 15, 1991,
                  abandoned, which is a continuation-in-part of Ser. No.
                  365,199, Jun. 12, 1989, Pat. No. 5,135,916.

=> s l7(P)(359 or 384)

          11918 359
          22504 384
L9            1 L7(P)(359 OR 384)

=> d l9 1


1.  5,843,884, Dec. 1, 1998, C9 complement inhibitor; Peter J. Sims,
514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2 [IMAGE AVAILABLE]

=> s l7(P)(complement)

          42870 COMPLEMENT
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L10 125 L7(P)(COMPLEMENT)

=> d l10 1-125

1. 5,843,884, Dec. 1, 1998, C9 complement inhibitor; Peter J. Sims, 514/2; 424/131.1, 138.1; 530/324, 387.1, 387.2 [IMAGE AVAILABLE]

2. 5,763,156, Jun. 9, 1998, Inhibition of complement mediated inflammatory response; Peter J. Sims, et al., 435/4, 2, 7.1, 7.2, 7.21, 29, 325, 366, 372, 374; 436/821; 604/7 [IMAGE AVAILABLE]

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17.6, 17.8, 17.9, 18.1, 118, 121, 122 [IMAGE AVAILABLE]

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=> d his

(FILE 'USPAT' ENTERED AT 09:20:29 ON 30 MAY 1999)
E SIMS, PETER ?/IN

L1 9 S E4,E5
L2 3 S L1 AND CD59
L3 0 S L2 AND (CD59)(P)(42 OR 58)
L4 3 S L2 AND (CD59)(P)(C9)
L5 4 S (CD59)(P)(42 OR 58)
L6 1 S C9(P)(ANTIBOD?)(P)(359 OR 384)
L7 125 S (C9)(P)(ANTIBOD?)(P)(INHIBIT? OR SUPPRESS? OR ANTAGONI?)
L8 3 S L7(P)(CD59)
L9 1 S L7(P)(359 OR 384)
L10 125 S L7(P)(COMPLEMENT)

=> d l10 116 -125 kwic

US PAT NO: 4,027,038 [IMAGE AVAILABLE] L10: 116 of 125

SUMMARY:

BSUM(5)

The **complement** system can be considered to consist of three sub-systems: (1) a recognition unit (C1q) which enables it to combine with **antibody** molecules that have detected a foreign invader; (2) an activation unit (C1r, C1s, C2, C4, C3), which prepares a site on the neighboring membrane; and (3) an attack unit (C5, C6, C7, C8 and **C9**) which creates a "hole" in the membrane. The membrane attack unit is non-specific; it destroys invaders only because it is. . . own cells, its activity must be limited in time. This limitation is accomplished partly by the spontaneous decay of activated **complement** and partly by interference by **inhibitors** and destructive enzymes. The control of **complement**, however, is not perfect, and there are times when damage is done to the host's cells. Immunity is therefore a. . .

US PAT NO: 5,843,884 [IMAGE AVAILABLE] L10: 1 of 125

SUMMARY:

BSUM(9)

In . . . Sims and Wiedmer disclose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . the vascular endothelium of organs and tissues to be transplanted are treated with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune disease states are treated by administering an effective amount of

a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclos[redacted]are methods for the productio[redacted] isolated polypeptides that are[redacted]le to **suppress complement** C5b[redacted]ediated platelet and endothelial cell activation.

DETDESC:

DETD(3)

Peptide sequence in human **complement** protein **C9** has been identified that contributes to the recognition of this protein by its naturally occurring **inhibitor**, CD59 . CD59 is known to bind to neo-epitopes that become exposed in **complement** C8 and **C9** during assembly of the cytolytic membrane attack complex of proteins C5b through **C9**. Through this interaction, CD59 interrupts assembly of the C5b-9 complex, protecting the target cell from destruction by these **complement** proteins. Data demonstrates that **antibody** raised against this human **C9**-derived peptide sequence is functionally **inhibitory** towards the lytic activity of the human C5b-9 complex. This permits design of reagents directed specifically at human **C9** that mimic or **inhibit** the **complement**-**inhibitory** function of cell-surface CD59.

DETDESC:

DETD(65)

The capacity of **antibody** against hu **C9** peptide 359-384 to **inhibit** MAC was determined by hemolytic assay, using the chE target cells described above, omitting CD59. In these experiments, 0-1 mg/ml Fab of **antibody** against hu **C9** peptide 359-384 (or, non-immune **antibody** control) was added with recombinant **C9** (hu, rb, or chimeric), and **complement**-specific lysis determined.

US PAT NO: 5,763,156 [IMAGE AVAILABLE] L10: 2 of 125

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . . collection and in vitro storage. Further, immune disease states can be treated by administering an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A method of monitoring the effectiveness of C5b-9 **inhibition** and subsequent platelet activation comprising exposing the platelets to be transfused to a membrane potentiometric fluorescent dye and comparing the. . . . Also disclosed are A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of

C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or [redacted]tibodies against C7 or **C9** whi[redacted]block the formation of the [redacted]-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of a-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets treated with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As . . . herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane

bound C5b-8. Similar results have been obtained in studies with erythrocytes and endo[redacted]lial cells. The requirement f[redacted]activated **C9** (incorporated into me[redacted]ane C5b-9 complexes) in the p[redacted]elet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

CLAIMS:

CLMS(2)

2. . . . wherein the platelets to be transfused have been treated prior to transfusion with a C5b-9 inactivator having the ability to **inhibit** C5b-9 mediated platelet or endothelial cell C5b-9 activation and cytolysis selected from the group consisting of an 18 kDa C5b-9 **inhibitory** protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that block **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface or membrane bound molecules in **inhibiting** C5b-9 activity, wherein the molecular weights are determined by SDS-PAGE under non-reducing conditions, and the **inhibitor** proteins are of the same origin as the **complement** proteins to be **inhibited**.

US PAT NO: 5,705,732 [IMAGE AVAILABLE] L10: 3 of 125

DETDESC:

DETD(28)

Sequential . . . non-lytic alteration of specific cell functions affecting vascular hemostases. In the case of human endothelial cells exposed to human serum **complement**, membrane deposition of the C5b-9 complex initiates a variety of procoagulant and prothrombotic changes in the cell that are expected to accelerate blood clotting and thrombus formation, as described, for example, by Hattori, et al., 1989 "**Complement** proteins C5b-9 induce secretion of high molecular weight multimers of endothelial von Willebrand Factor and translocation of granule membrane protein GMP-140 to the cell surface" J. Biol. Chem. 264:9053-9060; Hamilton, et al., 1990 "Regulatory control of the terminal **complement** proteins at the surface of human endothelial cells: Neutralization of a C5b-9 **inhibitor** by **antibody** to CD59" Blood 76:2572-2577; and Hamilton and Sims 1991 "The terminal **complement** proteins C5b-9 augment binding of high density lipoprotein and its apoproteins A-I and A-II to human endothelial cells" J. Clin. Invest. 88:1833-1840. These responses appear to depend upon insertion of **C9** into the plasma membrane of the target cell and therefore can be prevented by interfering with assembly of the C5b-9. . .

US PAT NO: 5,679,345 [IMAGE AVAILABLE] L10: 4 of 125

ABSTRACT:
Interference with formation of the **complement**-based membrane attack complex (MAC) will mitigate or even prevent tissue injury associated with the effects of **complement** in inflammation and graft rejection. Passive treatment of xenograft recipients at the time of and after transplantation with **antibody** against C-6, which interrupts the sequence of binding steps that form MAC, has been observed to **suppress** hyperacute xenograft rejection with no adverse signs or symptoms in the xenograft recipient. The present invention provides a method for. . . MAC formation in transplant recipients, by

administering compounds which interrupt one or more of the binding reactions between C5 d C6-**C9**, so that the MAC cann form.

SUMMARY:

BSUM(30)

The present invention provides a method for **suppressing complement**-dependent rejection of organ transplants comprising administering an **inhibitor** of membrane attack complex formation (MAC formation **inhibitor**) to an organ transplant recipient in an amount effective to **suppress** cell lysis initiated by formation of the C5b-**C9** membrane attack complex. The MAC formation **inhibitor** may be a non-functional C6 analog, a non-functional C7 analog, art anti-C6 **antibody**, an anti-C7 **antibody**, or the bacterial protein TraT, which **inhibits complement**-dependent cell lysis at the level of C6. In a particular embodiment, the method of this invention may be used to mitigate damage to an organ graft resulting from alternative pathway activation of **complement** in a graft recipient's serum by ischemically damaged tissue in the graft organ.

CLAIMS:

CLMS(1)

We claim:

1. A method of **suppressing complement**-dependent rejection of an organ transplant comprising administering an effective amount of an **inhibitor** of membrane attack complex formation (MAC formation **inhibitor**) to a recipient of a transplant organ wherein the **inhibitor** interferes with one or more binding steps in the sequential binding of **complement** component (C5b, C6, C7, C8, and **C9**, wherein the **inhibitor** is selected from the group consisting of a non-functional C6 analog, a non-functional C7 analog, an anti-C6 **antibody** and an anti-C7 **antibody**.

CLAIMS:

CLMS(15)

15. A method of **suppressing complement**-dependent rejection of organ transplants comprising infusing an isolated organ prior to transplant of said organ into an organ transplant recipient with an anti-C6 **antibody** or an anti-C7 **antibody** in an amount effective to **suppress** cell lysis initiated by formation of the C5b-**C9** membrane attack complex.

US PAT NO: 5,660,825 [IMAGE AVAILABLE] L10: 5 of 125

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . collection and in vitro storage. Further, immune disease states can be treated by administering an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent C9neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis. . . the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As . . . herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins

are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C[redacted]9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

CLAIMS:

CLMS(1)

We claim:

1. A method for the treatment of autoimmune disorders and other **complement**-mediated disease states in a patient requiring such treatment comprising:

administering an effective mount of a composition containing as the active agent a C5b-9 inactivator having the ability to **inhibit** C5b-9 mediated platelet or endothelial cell activation and cytolysis selected from the group consisting of an 18 kDa C5b-9 **inhibitory** protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, wherein the molecular weights are determined by SDS-PAGE under non-reducing conditions and the inactivator proteins are of the same origin as the **complement** proteins to be **inhibited**, monoclonal **antibodies** that block membrane binding of the C5b-9, monoclonal **antibodies** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that block **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface or membrane bound molecules in **inhibiting** C5b-9 activity; and

a pharmaceutically acceptable carrier.

US PAT NO: 5,635,178 [IMAGE AVAILABLE] L10: 6 of 125

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein isolated from human erythrocyte. . . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets treated with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GPIIb-IIIa, release of membrane microparticles from. . . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As . . . herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

SUMMARY:

BSUM(11)

In . . . Sims and Wiedmer disclose compositions and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain CD59, an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . . the vascular endothelium of organs and tissues to be transplanted are treated with these compositions to protect these cells from **complement** activation after transplantation. In another embodiment, immune disease states are treated by administering an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo. Also disclosed are methods for the production of isolated polypeptides that are able to **suppress complement** C5b-9 mediated platelet and endothelial cell activation.

SUMMARY:

BSUM(18)

This . . . the amplified gene expression in CD59-transfected CHO (Chinese Hamster Ovary) cells, which conferred protection on the cells from attack by **complement**. CD59 was stably expressed in Chinese hamster ovary cells using the pFRSV mammalian expression vector. After cloning and selection, the. . . . the sensitivity of the CD59 transfectants to the pore-forming activity of human C5b-9. Induction of cell-surface expression of CD59 antigen **inhibited** C5b-9 pore formation in a dose-dependent fashion. CD59 transfectants expressing greater than or equal to 1.3.times.10.sup.6 molecules of CD59/cell were completely resistant to human serum **complement**. By contrast, CD59 transfectants remained sensitive to the pore-forming activity of guinea pig C8 and **C9** (bound to human C5b-67). Functionally blocking **antibody** against erythrocyte CD59 abolished the human **complement** resistance observed for the CD59-transfected Chinese hamster ovary cells. These results confirm that the C5b-9 **inhibitory** function of the human erythrocyte membrane is provided by CD59 and that the gene for this protein can be expressed in xenotypic cells to confer protection against human serum **complement**.

DETDESC:

DETD(8)

As . . . filed Jun. 12, 1989, now U.S. Pat. No. 5,135,916 the conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response were based on the following. Addition of purified CD59, isolated from human erythrocyte membranes, to other blood cells or endothelium served to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of CD59, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which includes CD59. When bound

to the platelet surface, the Fab of .alpha.-P18 increases **C9** activation by membra[redacted]C5b-8, as monitored by exposu[redacted]f a complex-dependent **C9**[redacted]b-epitope. Although .alpha.-P[redacted]auses little increase in the cytolysis of platelets treated with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(60)

To demonstrate **complement inhibitory** activity, CD59 expression of transfected CHO cells was amplified by growth in 50 .mu.g/ml methotrexate: the cells were loaded with. . . FIG. 3. After washing, the cells were incubated (4.degree. C., 30 min) with either 0 mg/ml or 0.5 mg/ml functionally **inhibitory antibody** (Fab fragments) to CD59. Unbound **antibody** was removed; C8 (1 .mu.g/ml) and varying amounts of **C9**) were added; and dye release was measured after 15 min at 37.degree. C.

DETDESC:

DETD(61)

As shown in FIG. 4, the resistance to **complement**-mediated membrane damage observed for CD59-expressing CHO cells reflected **inhibition** of **C9**-dependent activation of the **complement** pore, and this **inhibition** was reversed by prior incubation of the cells with Fab fragments of a functionally blocking **antibody** directed against CD59 antigen. These data confirm that the protection against human serum **complement** observed for CD59 transfectants is related to the expression of cell-surface CD59 and is not due to other changes in. . .

US PAT NO: 5,550,108 [IMAGE AVAILABLE] L10: 8 of 125

ABSTRACT:
A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex. The compositions can be used in vitro to **inhibit** C5b-9 related stimulatory responses of platelets and vascular endothelium of perfused organs and tissues, thereby preventing the C5b-9 initiated cell. . . collection and in vitro storage. Further, immune disease states can be treated by administering an effective amount of a C5b-9 **inhibitor** to **suppress** C5b-9 mediated platelet activation in vivo.

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the

surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human othelial cells, active deriva[redacted]es or fragments thereof which act to **ibit** the activity of C5b-9, a[redacted]-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets treated with C5b-9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As . . . herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 **inhibitory** activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9, monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9, and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9.

DETDESC:

DETD(64)

Taken together, these data suggest that epitopes recognized by

.alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** to membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

US PAT NO: 5,135,916 [IMAGE AVAILABLE] L10: 9 of 125

SUMMARY:

BSUM(16)

A composition and methods for use thereof relating to polypeptides having the ability to act as an **inhibitor** of **complement** C5b-9 complex activity. The compositions contain an 18 kDa protein found on the surface of human erythrocytes, a 37 kDa. . . a 37 kDa protein found on the surface of human endothelial cells, active derivatives or fragments thereof which act to **inhibit** the activity of C5b-9, anti-idiotypic **antibodies** mimicking the action of the **inhibitor** proteins or **antibodies** against C7 or **C9** which block the formation of the C5b-9 complex.

DETDESC:

DETD(3)

The conclusions as to the mechanisms by which the platelet bound **inhibitor inhibits** the C5b-9 inflammatory response is based on the following. Addition of the purified 18 kDa protein, isolated from human erythrocyte. . . other blood cells or endothelium serves to protect these cells from both the cytolytic and cell-stimulatory effects of the C5b-9 **complement** proteins. The function of this 18 kDa C5b-9 **inhibitory** protein, when bound to platelet and endothelial cell surfaces, was also probed by raising a neutralizing (blocking) **antibody** (.alpha.-P18) that abrogates the C5b-9 **inhibitory** function of the purified molecule in vitro as well as the endogenous C5b-9 **inhibitory** factors, which may include the 18 kDa and 37 kDa proteins. When bound to the platelet surface, the FAB of .alpha.-P18 increases **C9** activation by membrane C5b-8, as monitored by exposure of a complex-dependent **C9** neo-epitope. Although .alpha.-P18 causes little increase in the cytolysis of platelets treated with C5b- 9 (as determined from the total release of lactate dehydrogenase of less than 5%), it markedly increases the cell stimulatory responses induced by these **complement** proteins, including secretion from platelet alpha and dense granules, conformational activation of cell surface GP IIb-IIIa, release of membrane microparticles. . . by approximately 10-fold the half-maximal concentration of C8 required to elicit each of these responses in the presence of excess **C9**. Incubation with .alpha.-P18 (Fab) alone does not activate platelets, nor does incubation with this **antibody** potentiate the stimulatory responses of platelets exposed to other agonists.

DETDESC:

DETD(4)

As . . . herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or **suppression** of **complement** mediated disorders, "C5b-9 inactivator"

refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 inhibitory activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal **antibodies** to C7 that block membrane binding of the C5b-9 , monoclonal **antibodies** to **C9** that block **C9** polymerization and insertion into the membrane, monoclonal **antibodies** that blocks **C9** binding to C5b-9 , and anti-idiotypic **antibodies** which **inhibit** the function of the cell surface molecules in **inhibiting** C5b-9 activity, especially the Fab fragments of monoclonal **antibodies** having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only **inhibitor** proteins of human origin will **inhibit** human C5b-9 .

DETDESC:

DETD(63)

Taken together, these data suggest that epitopes recognized by .alpha.-P18 include functional domains of a membrane component that **inhibits** formation of the C5b-9 **complement** pore, specifically by interfering with the binding and/or activation of **C9** by membrane bound C5b-8. Similar results have been obtained in studies with erythrocytes and endothelial cells. The requirement for activated **C9** (incorporated into membrane C5b-9 complexes) in the platelet responses observed in the presence of this **antibody** is underscored by the failure to detect significant platelet activation when either C8 alone (in the absence of **C9**) was added to C5b67 platelets exposed to .alpha.-P18 (Table II), or, when saturating amounts of **C9** were added to these platelets in the absence of added C8 (FIGS. 2,4,5).

US PAT NO: 4,820,635 [IMAGE AVAILABLE] L10: 10 of 125

SUMMARY:

BSUM(7)

Polyclonal **antibodies** directed to all of the neoantigens of SC5b-9 have been used in an immunoradiometric assay for SC5b-9 (Bhakdi and Muhly J. Immunol. Methods 57:283, 1983). This assay, which is based on the **inhibition** of binding of radiolabeled antineoantigen **antibodies** to rabbit erythrocyte membranes bearing MC5b-9 lesions, is sensitive to 3 to 4 .mu.g of SC5b-9 per ml, equivalent to a 1% activation of the terminal **complement** components in normal serum. In another competitive **inhibition** radioimmunoassay for SC5b-9 (Falk et al. Clin. Research 32:503A (abstract), 1984), a monoclonal **antibody** to the **C9** neoantigen was used. In this assay, radiolabeled polymerized **C9** was displaced from the monoclonal **antibody** by the SC5b-9 present in the test sample. A standard curve was created using unlabeled poly **C9**, and the results were expressed as unit equivalents of poly **C9** rather than as units of SC5b-9. The sensitivity of the assay was not reported. Finally, an enzyme-linked immunosorbent assay (ELISA) for SC5b-9 has been described which, in a sandwich fashion, uses **antibodies** to native epitopes in two different **complement** components present in the assembled C5b-9 complex. Although this approach yields a sensitive assay for SC5b-9, the utility of the assay is limited in that its signal can be **inhibited** by normal human serum (Mollnes et al. Scand. J. Immunol. 20:157, 1984).

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Last logoff:  27may99 12:46:51
Logon file001 30may99 08:43:22
ANNOUNCEMENT    ****    ANNOUNCEMENT    ****    ANNOUNCEMENT
NEW
***Miller Freeman Industry and Product News (File 112)
***Irish Times (File 477)
***Business Wire (Files 610 for current news & 810 for archive news)
***PR Newswire (Files 613 for current news & 813 for archive news)
***U.S. Newswire (Files 605 for current news & 665 for archive news)
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       30may99 08:43:29 User208760 Session D1243.1
            $0.27    0.083 DialUnits File1
     $0.27  Estimated cost File1
            FTSNET   0.016 Hrs.
     $0.27  Estimated cost this search
     $0.27  Estimated total session cost   0.083 DialUnits

File 410:Chronolog(R)  1981-1999 May/Jun
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         $0.00  Estimated cost File410
                FTSNET   0.003 Hrs.
         $0.00  Estimated cost this search
         $0.27  Estimated total session cost   0.124 DialUnits

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  File  55:Biosis Preiviews(R)  1993-1999/May W4
         (c) 1999 BIOSIS
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*File  72: EMBASE reloaded. Accession numbers have changed.
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E1        0 *AU=SIMS, PETER ?
E2       74  AU=SIMS, PETER J.
E3        5  AU=SIMS, PETER JAY
E4        1  AU=SIMS, PETER S.
E5       14  AU=SIMS, PETER STANFORD
E6        4  AU=SIMS, PHILIP F.
E7        1  AU=SIMS, PHILIP FRANKLIN
E8        1  AU=SIMS, PHILLIP F.
E9        1  AU=SIMS, PHILLIP L.
E10      11  AU=SIMS, R.
E11       7  AU=SIMS, R. A.
E12      19  AU=SIMS, R. C.

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? s e2,e3

              74  AU=SIMS, PETER J.
               5  AU=SIMS, PETER JAY
      S1      79  E2,E3
? rd s1

...examined 50 records  (50)
...completed examining records
      S2      78  RD S1 (unique items)
? s s2 and (cd59 or c9

>>>Unmatched parentheses
? s s2 and (cd59 or c9)

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            2102  CD59
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             4106  C9
      S3       25  S2      (CD59 OR C9)
? t s3/3/all
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3/3/1 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129066658 CA: 129(6)66658j JOURNAL
Identity of the residues responsible for the species-restricted complement inhibitory function of human CD59
AUTHOR(S): Zhao, Xiao-Jian; Zhao, Ji; Zhou, Quansheng; Sims, Peter J.
LOCATION: The Blood Center, Blood Research Institute, Milwaukee, WI, 53201-2178, USA
JOURNAL: J. Biol. Chem. DATE: 1998 VOLUME: 273 NUMBER: 17 PAGES: 10665-10671 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology

3/3/2 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

128106392 CA: 128(9)106392f PATENT
Genetically engineered cells as universal donor cells for vascular grafts or drug delivery
INVENTOR(AUTHOR): Sims, Peter J.; Bothwell, Alfred L.; Elliot, Eileen A.; Flavell, Richard A.; Madri, Joseph; Rollins, Scott; Bell, Leonard; Squinto, Stephen
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation; Yale University
PATENT: United States ; US 5705732 A DATE: 19980106
APPLICATION: US 87007 (19930701) *US 365199 (19890612) *US 729926 (19910715) *US 906394 (19920629) *US 271562 (19940707)
PAGES: 35 pp. Cont.-in-part of U.S. Ser. No. 906,394, abandoned. CODEN: USXXAM LANGUAGE: English CLASS: 800002000; C12N-015/00A; C07H-021/02B

3/3/3 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

126276124 CA: 126(21)276124w JOURNAL
Structure-function relationships of the complement regulatory protein, CD59
AUTHOR(S): Petranka, John; Zhao, Ji; Norris, John; Tweedy, Neil B.; Ware, Russell E.; Sims, Peter J.; Rosse, Wendell F.
LOCATION: Divisions of Hematology/Oncology, Departments of Medicine and Pediatrics,, Duke University Medical Center, Durham, NC, 27710, USA
JOURNAL: Blood Cells, Mol. Dis. DATE: 1996 VOLUME: 22 NUMBER: 3
PAGES: 281-296 CODEN: BCMDFX ISSN: 1079-9796 LANGUAGE: English
PUBLISHER: Academic

3/3/4 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

126262879 CA: 126(20)262879j JOURNAL
Expression of recombinant CD59 with an N-terminal peptide epitope facilitates analysis of residues contributing to its complement-inhibitory function
AUTHOR(S): Zhou, Quansheng; Zhao, Ji; Husler, Thomas; Sims, Peter J.
LOCATION: Blood Center Southeastern Wisconsin, Blood Res. Inst.,

Milwaukee, WI, 53201, USA
JOURNAL: Mol. Immun[redacted] DATE: 1996 VOLUME: 33 NUM[redacted] 14 PAGES: 1127-1134 CODEN: MO[redacted] ISSN: 0161-5890 PUBLISHER [redacted] IDENTIFIER: 0161-5890(96)00074-0 LANGUAGE: English PUBLISHER: Elsevier

3/3/5 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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126155551 CA: 126(12)155551z JOURNAL
Complement C5b-9 increases plasminogen binding and activation on human endothelial cells
AUTHOR(S): Christiansen, Victoria J.; Sims, Peter J.; Hamilton, Karen K.
LOCATION: Department of Medicine and William K. Warren Medical Research Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA
JOURNAL: Arterioscler., Thromb., Vasc. Biol. DATE: 1997 VOLUME: 17 NUMBER: 1 PAGES: 164-171 CODEN: ATVBFA ISSN: 1079-5642 LANGUAGE: English PUBLISHER: American Heart Association

3/3/6 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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125245265 CA: 125(19)245265t JOURNAL
Elimination of potential sites of glycosylation fails to abrogate complement regulatory function of cell surface CD59
AUTHOR(S): Rother, Russell P.; Zhao, Ji; Zhou, Quansheng; Sims, Peter J.
LOCATION: Alexion Pharmaceuticals Inc., New Haven, CT, 06511, USA
JOURNAL: J. Biol. Chem. DATE: 1996 VOLUME: 271 NUMBER: 39 PAGES: 23842-23845 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/7 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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124143160 CA: 124(11)143160s JOURNAL
Role of a Disulfide-Bonded Peptide Loop within Human Complement C9 in the Species-Selectivity of Complement Inhibitor CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Sims, Peter J.
LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: Biochemistry DATE: 1996 VOLUME: 35 NUMBER: 10 PAGES: 3263-9
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English

3/3/8 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1999 American Chemical Society. All rts. reserv.

123225489 CA: 123(17)225489z JOURNAL
Identity of the segment of human complement C8 recognized by complement regulatory protein CD59
AUTHOR(S): Lockert, Dara H.; Kaufman, Kenneth M.; Chang, Chi-Pei; Husler, Thomas; Sodetz, James M.; Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: J. Biol. Chem. DATE: 1995 VOLUME: 270 NUMBER: 34 PAGES: 19723-8 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/9 (Item 9 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)
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122211724 CA: 122(17)211724q JOURNAL
Chimeras of human complement C9 reveal the site recognized by complement regulatory protein CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Kaufman, Kenneth M.; Sodetz, James M.; Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeast. Wisconsin, Milwaukee, WI, 53201-2178, USA
JOURNAL: J. Biol. Chem. DATE: 1995 VOLUME: 270 NUMBER: 8 PAGES: 3483-6 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/10 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1999 American Chemical Society. All rts. reserv.

121228383 CA: 121(19)228383e JOURNAL
Identity of a peptide domain of human C9 that is recognized by the cell-surface complement inhibitor, CD59
AUTHOR(S): Chang, Chi-Pei; Huesler, Thomas; Zhao, Ji; Wiedmer, Therese; Sims, Peter J.
LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: J. Biol. Chem. DATE: 1994 VOLUME: 269 NUMBER: 42 PAGES: 26424-30 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/11 (Item 11 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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121202810 CA: 121(17)202810s JOURNAL
CD59 costimulation of T cell activation. CD58 dependence and requirement for glycosylation
AUTHOR(S): Menu, Elisabeth; Tsai, Betsy C.; Bothwell, Alfred L. M.; Sims, Peter J.; Bierer, Barbara E.
LOCATION: Division of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, 02115, USA
JOURNAL: J. Immunol. DATE: 1994 VOLUME: 153 NUMBER: 6 PAGES: 2444-56
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English

3/3/12 (Item 12 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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121131942 CA: 121(11)131942y JOURNAL
Protection of porcine aortic endothelial cells from complement-mediated cell lysis and activation by recombinant human CD59
AUTHOR(S): Kennedy, Scott P.; Rollins, Scott A.; Burton, Willis V.; Sims, Peter J.; Bothwell, Alfred L. M.; Squinto, Stephen P.; Zavoico, George B.
LOCATION: Dep. Vasc. Biol., Alexion Pharm., Inc., New Haven, CT, 06511, USA
JOURNAL: Transplantation DATE: 1994 VOLUME: 57 NUMBER: 10 PAGES: 1494-501 CODEN: TRPLAU ISSN: 0041-1337 LANGUAGE: English

3/3/13 (Item 13 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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121032591 CA: 121(3)32591b JOURNAL
Structure and function of CD59

AUTHOR(S): Sims, Peter J.
LOCATION: Blood Re[redacted] Inst., Blood Cent. Southeast.[redacted]s., Milwaukee, WI, 53233, USA
JOURNAL: Int. Congr. Ser. - Excerpta Med. DATE: 1993 VOLUME: 1042
NUMBER: BIOLOGY OF VITRONECTINS AND THEIR RECEPTORS PAGES: 243-8
CODEN: EXMDA4 ISSN: 0531-5131 LANGUAGE: English

3/3/14 (Item 14 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

118167044 CA: 118(17)167044j JOURNAL
Interaction between apolipoproteins A-I and A-II and the membrane attack complex of complement. Affinity of the apoproteins for polymeric C9
AUTHOR(S): Hamilton, Karen K.; Zhao, Ji; Sims, Peter J.
LOCATION: Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1993 VOLUME: 268 NUMBER: 5 PAGES: 3632-8 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/15 (Item 15 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117169646 CA: 117(19)169646f JOURNAL
Inhibition of the complement membrane attack complex by the galactose-specific adhesin of Entamoeba histolytica
AUTHOR(S): Braga, Lucia L.; Ninomiya, Haruhiko; McCoy, James J.; Eacker, Suzanne; Wiedmer, Therese; Pham, Christine; Wood, Sheila; Sims, Peter J.; Petri, William A., Jr.
LOCATION: Sch. Med., Univ. Virginia, Charlottesville, VA, 22908, USA
JOURNAL: J. Clin. Invest. DATE: 1992 VOLUME: 90 NUMBER: 3 PAGES: 1131-7 CODEN: JCINAO ISSN: 0021-9738 LANGUAGE: English

3/3/16 (Item 16 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117088287 CA: 117(9)88287s JOURNAL
The human complement regulatory protein CD59 binds to the .alpha.-chain of C8 and to the "b" domain of C9
AUTHOR(S): Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1992 VOLUME: 267 NUMBER: 19 PAGES: 13675-80 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/17 (Item 17 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117088212 CA: 117(9)88212p JOURNAL
Overlapping but nonidentical binding sites on CD2 for CD58 and a second ligand CD59
AUTHOR(S): Hahn, William C.; Menu, Elisabeth; Bothwell, Alfred L. M.; Sims, Peter J.; Bierer, Barbara E.
LOCATION: Div. Pediatr. Oncol., Dana-Farber Cancer Inst., Boston, MA, 02115, USA
JOURNAL: Science (Washington, D. C., 1883-) DATE: 1992 VOLUME: 256
NUMBER: 5065 PAGES: 1805-7 CODEN: SCIEAS ISSN: 0036-8075 LANGUAGE: English

3/3/18 (Item 18 [redacted]m file: 399)
DIALOG(R)File 399:CA [redacted]RCH(R)

116253695 CA: 116(25)253695n JOURNAL
Contribution of the N-linked carbohydrate of erythrocyte antigen CD59 to its complement-inhibitory activity
AUTHOR(S): Ninomiya, Haruhiko; Stewart, Betty H.; Rollins, Scott A.; Zhao, Ji; Bothwell, Alfred L. M.; Sims, Peter J.
LOCATION: Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1992 VOLUME: 267 NUMBER: 12 PAGES: 8404-10 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

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3/3/19 (Item 19 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

115133684 CA: 115(13)133684r JOURNAL
Inhibition of homologous complement by CD59 is mediated by a species-selective recognition conferred through binding to C8 within C5b-8 or C9 within C5b-9
AUTHOR(S): Rollins, Scott A.; Zhao, Ji; Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1991 VOLUME: 146 NUMBER: 7 PAGES: 2345-51
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English

3/3/20 (Item 20 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

115129040 CA: 115(13)129040k JOURNAL
Amplified gene expression in CD59-transfected Chinese hamster ovary cells confers protection against the membrane attack complex of human complement
AUTHOR(S): Zhao, Ji; Rollins, Scott A.; Maher, Stephen E.; Bothwell, Alfred L. M.; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1991 VOLUME: 266 NUMBER: 20 PAGES: 13418-22 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

3/3/21 (Item 21 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

114099628 CA: 114(11)99628t JOURNAL
Regulatory control of the terminal complement proteins at the surface of human endothelial cells: neutralization of a C5b-9 inhibitor by antibody to CD59
AUTHOR(S): Hamilton, Karen K.; Ji, Zhao; Rollins, Scott; Stewart, Betty H.; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, USA
JOURNAL: Blood DATE: 1990 VOLUME: 76 NUMBER: 12 PAGES: 2572-7
CODEN: BLOOAW ISSN: 0006-4971 LANGUAGE: English

3/3/22 (Item 22 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

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113057087 CA: 11[redacted])57087q JOURNAL
The complement-inhibitory activity of CD59 resides in its capacity to block incorporation of C9 into membrane C5b-9
AUTHOR(S): Rollins, Scott A.; Sims, Peter J.
LOCATION: Health Sci. Cent., Oklahoma Univ., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1990 VOLUME: 144 NUMBER: 9 PAGES: 3478-83
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English

3/3/23 (Item 23 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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101037054 CA: 101(5)37054a JOURNAL
Kinetics of polymerization of a fluoresceinated derivative of complement protein C9 by the membrane-bound complex of complement proteins C5b-8
AUTHOR(S): Sims, Peter Jay; Wiedmer, Therese
LOCATION: Med. Sch., Univ. Virginia, Charlottesville, VA, 22908, USA
JOURNAL: Biochemistry DATE: 1984 VOLUME: 23 NUMBER: 14 PAGES: 3260-7
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English

3/3/24 (Item 24 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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101037053 CA: 101(5)37053z JOURNAL
Complement protein C9 labeled with fluorescein isothiocyanate can be used to monitor C9 polymerization and formation of the cytolytic membrane lesion
AUTHOR(S): Sims, Peter Jay
LOCATION: Med. Sch., Univ. Virginia, Charlottesville, VA, 22908, USA
JOURNAL: Biochemistry DATE: 1984 VOLUME: 23 NUMBER: 14 PAGES: 3248-60
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English

3/3/25 (Item 25 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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99103484 CA: 99(13)103484j JOURNAL
Complement pores in erythrocyte membranes. Analysis of C8/C9 binding required for functional membrane damage
AUTHOR(S): Sims, Peter J.
LOCATION: Med. Cent., Univ. Virginia, Charlottesville, VA, 22908, USA
JOURNAL: Biochim. Biophys. Acta DATE: 1983 VOLUME: 732 NUMBER: 3
PAGES: 541-52 CODEN: BBACAQ ISSN: 0006-3002 LANGUAGE: English

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          3327  384
          2644  359
     S4      0  S3 AND (384 OR 359)
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3/7/1 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 1999 American Chemical Society. All rts. reserv.

129066658 CA: 129(6)66658j JOURNAL
Identity of the residues responsible for the species-restricted complement inhibitory function of human CD59

AUTHOR(S): Zhao, Xiao-Jian; Zhao, Ji; Zhou, Quansheng; Sims, Peter J.
LOCATION: The Bloo nter, Blood Research Institut Milwaukee, WI, 53201-2178, USA
JOURNAL: J. Biol. Chem. DATE: 1998 VOLUME: 273 NUMBER: 17 PAGES: 10665-10671 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English PUBLISHER: American Society for Biochemistry and Molecular Biology
SECTION:
CA215004 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: complement inhibitory function CD59 species restriction, antigen CD59 cDNA sequence rabbit
DESCRIPTORS:
Protein sequences...
homol.; identity of residues responsible for species-restricted complement inhibitory function of human CD59 and sequence of rabbit CD59 cDNA
cDNA sequences... CD59(antigen)... Protein motifs... Protein sequences... Rabbit... Solution structure... Species differences...
identity of residues responsible for species-restricted complement inhibitory function of human CD59 and sequence of rabbit CD59 cDNA
CAS REGISTRY NUMBERS:
208879-37-2 amino acid sequence; identity of residues responsible for species-restricted complement inhibitory function of human CD59 and sequence of rabbit CD59 cDNA
80295-58-5 80295-59-6 82986-89-8 identity of residues responsible for species-restricted complement inhibitory function of human CD59 and sequence of rabbit CD59 cDNA
208920-99-4 nucleotide sequence; identity of residues responsible for species-restricted complement inhibitory function of human CD59 and sequence of rabbit CD59 cDNA

3/7/2 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

128106392 CA: 128(9)106392f PATENT
Genetically engineered cells as universal donor cells for vascular grafts or drug delivery
INVENTOR(AUTHOR): Sims, Peter J.; Bothwell, Alfred L.; Elliot, Eileen A.; Flavell, Richard A.; Madri, Joseph; Rollins, Scott; Bell, Leonard; Squinto, Stephen
LOCATION: USA
ASSIGNEE: Oklahoma Medical Research Foundation; Yale University
PATENT: United States ; US 5705732 A DATE: 19980106
APPLICATION: US 87007 (19930701) *US 365199 (19890612) *US 729926 (19910715) *US 906394 (19920629) *US 271562 (19940707)
PAGES: 35 pp. Cont.-in-part of U.S. Ser. No. 906,394, abandoned. CODEN: USXXAM LANGUAGE: English CLASS: 800002000; C12N-015/00A; C07H-021/02B
SECTION:
CA263003 Pharmaceuticals
CA203XXX Biochemical Genetics
CA215XXX Immunochemistry
IDENTIFIERS: genetic engineering transplant animal cell, histocompatibility antigen recombinant cell transplantation, protein inhibiting complement recombinant cell transplantation, CD59 antigen recombinant cell transplantation, vascular graft recombinant cell complement resistance
DESCRIPTORS:
Vascular endothelium...
aortic; genetically engineered cells as universal donor cells for vascular grafts or drug delivery by inhibition of complement-mediated lysis
Hematopoietic precursor cell...
BFU-MF, CD50 gene expression in protection against activation of lysis

Prosthetic implants...
cardiovascular i nts; genetically engineered c s as universal donor cells for ular grafts or drug delivery inhibition of complement-mediated lysis
Blood cells... Hematopoietic precursor cell...
CD59 antigen gene expression on
Fluoropolymers,biological studies...
CD59 antigen gene-expressing recombinant porcine aortic endothelial cells attachment to
Hematopoietic precursor cell...
CFU-L, CD50 gene expression in protection against activation of lysis
Proteins(specific proteins and subclasses)...
complement-regulating; genetically engineered cells as universal donor cells for vascular grafts or drug delivery
Aorta...
endothelium; genetically engineered cells as universal donor cells for vascular grafts or drug delivery by inhibition of complement-mediated lysis
cDNA sequences...
for CD59 antigen cDNA of human genetically engineered cells as universal donor cells for vascular grafts or drug delivery
Epithelium... Mammalian cells... Organ(animal)... Prostheses... Swine...
Transplant(organ)...
genetically engineered cells as universal donor cells for vascular grafts or drug delivery
BFU-E(burst-forming unit-erythroid)... CD59(antigen)...
CFU-S(colony-forming unit-spleen)... Class I MHC antigens... Class II MHC antigens... Complement... Gene therapy... Membrane cofactor protein...
Vascular endothelium...
genetically engineered cells as universal donor cells for vascular grafts or drug delivery by inhibition of complement-mediated lysis
Protein sequences...
of CD59 antigen cDNA of human genetically engineered cells as universal donor cells for vascular grafts or drug delivery
Platelet(blood)...
recombinant cell expressing gene for CD59 antigen for activation of endothelial and platelet cells by complement
Animal...
transgenic nonhuman cells expressing gene for protein inhibiting attack by complement but lacking gene for MHC antigen
CAS REGISTRY NUMBERS:
9002-84-0 CD59 antigen gene-expressing recombinant porcine aortic endothelial cells attachment to
82986-89-8 CHO cells transfected with gene for CD59 antigen of human protection against lysis by
99085-47-9P 126546-13-2 147155-21-3P genetically engineered cells as universal donor cells for vascular grafts or drug delivery

3/7/3 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

126276124 CA: 126(21)276124w JOURNAL
Structure-function relationships of the complement regulatory protein, CD59
AUTHOR(S): Petranka, John; Zhao, Ji; Norris, John; Tweedy, Neil B.; Ware, Russell E.; Sims, Peter J.; Rosse, Wendell F.
LOCATION: Divisions of Hematology/Oncology, Departments of Medicine and Pediatrics,, Duke University Medical Center, Durham, NC, 27710, USA
JOURNAL: Blood Cells, Mol. Dis. DATE: 1996 VOLUME: 22 NUMBER: 3
PAGES: 281-296 CODEN: BCMDFX ISSN: 1079-9796 LANGUAGE: English
PUBLISHER: Academic
SECTION:
CA215004 Immunochemistry

IDENTIFIERS: CD59 structure function disulfide bond epitope
DESCRIPTORS:
CD59(antigen)... Epit[redacted]s... Structure-activity relat[redacted]ship...
structure-function relationships of complement regulatory protein, CD59
Bond...
sulfur-sulfur; structure-function relationships of complement regulatory protein, CD59

3/7/4 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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126262879 CA: 126(20)262879j JOURNAL
Expression of recombinant CD59 with an N-terminal peptide epitope facilitates analysis of residues contributing to its complement-inhibitory function
AUTHOR(S): Zhou, Quansheng; Zhao, Ji; Husler, Thomas; Sims, Peter J.
LOCATION: Blood Center Southeastern Wisconsin, Blood Res. Inst., Milwaukee, WI, 53201, USA
JOURNAL: Mol. Immunol. DATE: 1996 VOLUME: 33 NUMBER: 14 PAGES: 1127-1134 CODEN: MOIMD5 ISSN: 0161-5890 PUBLISHER ITEM IDENTIFIER: 0161-5890(96)00074-0 LANGUAGE: English PUBLISHER: Elsevier
SECTION:
CA215002 Immunochemistry
IDENTIFIERS: CD59 structure complement inhibition
DESCRIPTORS:
Amino acids,biological studies... CD59(antigen)... Complement...
amino acid residues that are important for the complement-inhibitory function of CD59
Structure-activity relationship...
complement-inhibiting; amino acid residues that are important for the complement-inhibitory function of CD59
CAS REGISTRY NUMBERS:
60-18-4 63-68-3 biological studies, amino acid residues that are important for the complement-inhibitory function of CD59

3/7/5 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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126155551 CA: 126(12)155551z JOURNAL
Complement C5b-9 increases plasminogen binding and activation on human endothelial cells
AUTHOR(S): Christiansen, Victoria J.; Sims, Peter J.; Hamilton, Karen K.
LOCATION: Department of Medicine and William K. Warren Medical Research Institute, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA
JOURNAL: Arterioscler., Thromb., Vasc. Biol. DATE: 1997 VOLUME: 17 NUMBER: 1 PAGES: 164-171 CODEN: ATVBFA ISSN: 1079-5642 LANGUAGE: English PUBLISHER: American Heart Association
SECTION:
CA213005 Mammalian Biochemistry
IDENTIFIERS: endothelium plasminogen binding complement C5b9 C9
DESCRIPTORS:
Vascular endothelium...
complement C5b-9 increases plasminogen binding and activation on human endothelial cells
Peptides,biological studies...
20-amino acid carboxyl terminus of C9; carboxyl-terminal lysine of C9 enhance plasminogen activation by tissue-type plasminogen activator
CAS REGISTRY NUMBERS:
56-87-1 biological studies, carboxyl-terminal lysine of C9 enhance plasminogen activation by tissue-type plasminogen activator

7440-70-2 biological studies, effect on plasminogen binding to human endothelial cells
9001-91-6 82986-89-8 101754-00-1 139639-23-9 complement C5b-9 increases plasminogen binding and activation on human endothelial cells
80295-59-6 enhance plasminogen activation by tissue-type plasminogen activator
80295-57-4 plasminogen specifically to C7 and C9

3/7/6 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

125245265 CA: 125(19)245265t JOURNAL
Elimination of potential sites of glycosylation fails to abrogate complement regulatory function of cell surface CD59
AUTHOR(S): Rother, Russell P.; Zhao, Ji; Zhou, Quansheng; Sims, Peter J.
LOCATION: Alexion Pharmaceuticals Inc., New Haven, CT, 06511, USA
JOURNAL: J. Biol. Chem. DATE: 1996 VOLUME: 271 NUMBER: 39 PAGES: 23842-23845 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 glycosylation site complement regulatory function
DESCRIPTORS:
Glycosidation...
glycosylation of CD59 in relation to the complement regulatory function of CD59
Antigens,CD59...
glycosylation sites on CD59 in relation to the complement regulatory function of CD59
CAS REGISTRY NUMBERS:
82986-89-8 glycosylation sites on CD59 in relation to the complement regulatory function of CD59

3/7/7 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

124143160 CA: 124(11)143160s JOURNAL
Role of a Disulfide-Bonded Peptide Loop within Human Complement C9 in the Species-Selectivity of Complement Inhibitor CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Sims, Peter J.
LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: Biochemistry DATE: 1996 VOLUME: 35 NUMBER: 10 PAGES: 3263-9
CODEN: BICHAW ISSN: 0006-2960 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 disulfide bonded loop CD59
DESCRIPTORS:
Antigens,CD59... Cytolysis... Disulfide group... Molecular association... Molecular structure-biological activity relationship...
human complement C9 disulfide-bonded peptide loop in the species-selectivity of complement inhibitor CD59
CAS REGISTRY NUMBERS:
80295-59-6 human complement C9 disulfide-bonded peptide loop in the species-selectivity of complement inhibitor CD59

3/7/8 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

123225489 CA: 123(17)225489z JOURNAL

Identity of the segment of human complement C8 recognized by complement regulatory protein C[redacted]
AUTHOR(S): Lockert[redacted]ara H.; Kaufman, Kenneth M.; [redacted]g, Chi-Pei; Husler, Thomas; Sodetz, James M.; Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: J. Biol. Chem. DATE: 1995 VOLUME: 270 NUMBER: 34 PAGES: 19723-8 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C8 recognition protein CD59
DESCRIPTORS:
Antigens,CD59...
human complement C8 domain recognized by complement regulatory protein CD59
CAS REGISTRY NUMBERS:
80295-58-5 168147-61-3 human complement C8 domain recognized by complement regulatory protein CD59

3/7/9 (Item 9 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

122211724 CA: 122(17)211724q JOURNAL
Chimeras of human complement C9 reveal the site recognized by complement regulatory protein CD59
AUTHOR(S): Huesler, Thomas; Lockert, Dara H.; Kaufman, Kenneth M.; Sodetz, James M.; Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeast. Wisconsin, Milwaukee, WI, 53201-2178, USA
JOURNAL: J. Biol. Chem. DATE: 1995 VOLUME: 270 NUMBER: 8 PAGES: 3483-6 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: complement C9 recognition sequence protein CD59, sequence complement C9 rabbit
DESCRIPTORS:
Antigens,CD59... Deoxyribonucleic acid sequences,complementary... Gene,animal... Protein sequences... Rabbit...
chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
CAS REGISTRY NUMBERS:
161631-71-6 amino acid sequence; chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
80295-59-6 chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59
161657-70-1 nucleotide sequence; chimeras of human complement C9 reveal site recognized by complement regulatory protein CD59

3/7/10 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121228383 CA: 121(19)228383e JOURNAL
Identity of a peptide domain of human C9 that is recognized by the cell-surface complement inhibitor, CD59
AUTHOR(S): Chang, Chi-Pei; Huesler, Thomas; Zhao, Ji; Wiedmer, Therese; Sims, Peter J.
LOCATION: Blood Research Institute, Blood Center of Southeastern Wisconsin, Milwaukee, WI, 53233, USA
JOURNAL: J. Biol. Chem. DATE: 1994 VOLUME: 269 NUMBER: 42 PAGES: 26424-30 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English

SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 CD59 binding region
DESCRIPTORS:
Molecular structure-biological activity relationship...
CD59-binding; of complement C9
Antigens,CD59... Peptides,biological studies...
identity of a peptide domain of human C9 that is recognized by CD59
CAS REGISTRY NUMBERS:
80295-59-6 identity of a peptide domain of human C9 that is recognized by CD59

3/7/11 (Item 11 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121202810 CA: 121(17)202810s JOURNAL
CD59 costimulation of T cell activation. CD58 dependence and requirement for glycosylation
AUTHOR(S): Menu, Elisabeth; Tsai, Betsy C.; Bothwell, Alfred L. M.; Sims, Peter J.; Bierer, Barbara E.
LOCATION: Division of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, 02115, USA
JOURNAL: J. Immunol. DATE: 1994 VOLUME: 153 NUMBER: 6 PAGES: 2444-56
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215002 Immunochemistry
IDENTIFIERS: CD59 CD58 T lymphocyte proliferation glycosylation
DESCRIPTORS:
Antigens,CD58... Antigens,CD59... Cell proliferation... Lymphocyte,T-cell ... Lymphokines and Cytokines,interleukin 2...
CD58 and glycosylation required for CD59-enhanced T cell activation
Glycosidation...
CD58 glycosylation required for CD59-enhanced T cell activation

3/7/12 (Item 12 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121131942 CA: 121(11)131942y JOURNAL
Protection of porcine aortic endothelial cells from complement-mediated cell lysis and activation by recombinant human CD59
AUTHOR(S): Kennedy, Scott P.; Rollins, Scott A.; Burton, Willis V.; Sims, Peter J.; Bothwell, Alfred L. M.; Squinto, Stephen P.; Zavoico, George B.
LOCATION: Dep. Vasc. Biol., Alexion Pharm. Inc., New Haven, CT, 06511, USA
JOURNAL: Transplantation DATE: 1994 VOLUME: 57 NUMBER: 10 PAGES: 1494-501 CODEN: TRPLAU ISSN: 0041-1337 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 antigen swine vascular endothelium complement
DESCRIPTORS:
Transplant and Transplantation,xeno-...
complement cytolytic and procoagulant activity inhibition by transgenic human CD59 antigen on vascular endothelium in relation to
Antibodies...
complement-mediated cytolysis of porcine vascular endothelium activated by, transgenic human CD59 antigen inhibition of
Cytolysis...
complement-mediated, transgenic human CD59 antigen on porcine vascular endothelium inhibition of
Complement...
cytolysis by, transgenic human CD59 antigen on porcine vascular

endothelium inhibition of
Artery,aorta, endoth[redacted]um,composition...
transgenic human[redacted]59 antigen on porcine, comple[redacted]t cytolytic and procoagulant activity inhibition by
Swine...
transgenic human CD59 antigen on vascular endothelium of, complement cytolytic and procoagulant activity inhibition by, xenotransplantation in relation to
Antigens,CD59...
transgenic human, on porcine vascular endothelium, complement cytolytic and procoagulant activity inhibition by
CAS REGISTRY NUMBERS:
72162-96-0 activation of, by terminal complement complex, transgenic human CD59 antigen on porcine vascular endothelium inhibition of, xenotransplantation in relation to
82986-89-8 procoagulant activity of, transgenic human CD59 antigen on porcine vascular endothelium inhibition of, xenotransplantation in relation to

3/7/13 (Item 13 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121032591 CA: 121(3)32591b JOURNAL
Structure and function of CD59
AUTHOR(S): Sims, Peter J.
LOCATION: Blood Res. Inst., Blood Cent. Southeast. Wis., Milwaukee, WI, 53233, USA
JOURNAL: Int. Congr. Ser. - Excerpta Med. DATE: 1993 VOLUME: 1042
NUMBER: BIOLOGY OF VITRONECTINS AND THEIR RECEPTORS PAGES: 243-8
CODEN: EXMDA4 ISSN: 0531-5131 LANGUAGE: English
SECTION:
CA215000 Immunochemistry
IDENTIFIERS: CD59 structure function review
DESCRIPTORS:
Antigens,CD59...
structure and function of

3/7/14 (Item 14 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

118167044 CA: 118(17)167044j JOURNAL
Interaction between apolipoproteins A-I and A-II and the membrane attack complex of complement. Affinity of the apoproteins for polymeric C9
AUTHOR(S): Hamilton, Karen K.; Zhao, Ji; Sims, Peter J.
LOCATION: Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1993 VOLUME: 268 NUMBER: 5 PAGES: 3632-8 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 apolipoprotein AI AII binding
DESCRIPTORS:
Lipoproteins,apo-, A-I... Lipoproteins,apo-, A-II...
complement C9 polymers binding to
CAS REGISTRY NUMBERS:
80295-59-6D complexes, with complement C5b, apolipoprotein A-I and A-II binding to C9 polymers within
80295-55-2D complexes, with complement C9, apolipoprotein A-I and A-II binding to C9 polymers within

3/7/15 (Item 15 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117189848 CA: 117(19)189848f JOURNAL
Inhibition of the complement membrane attack complex by the galactose-specific adhesin of Entamoeba histolytica
AUTHOR(S): Braga, Lucia L.; Ninomiya, Haruhiko; McCoy, James J.; Eacker, Suzanne; Wiedmer, Therese; Pham, Christine; Wood, Sheila; Sims, Peter J.; Petri, William A., Jr.
LOCATION: Sch. Med., Univ. Virginia, Charlottesville, VA, 22908, USA
JOURNAL: J. Clin. Invest. DATE: 1992 VOLUME: 90 NUMBER: 3 PAGES: 1131-7 CODEN: JCINAO ISSN: 0021-9738 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement attack complex galactose adhesin Entamoeba
DESCRIPTORS:
Cytolysis...
complement-mediated, inhibition of, by galactose-specific adhesin of Entamoeba histolytica
Entamoeba histolytica...
galactose-specific adhesin of, complement membrane attack complex inhibition by
Antigens,CD59...
galactose-specific adhesin of Entamoeba histolytica homol. with
Adhesins...
galactose-specific, of Entamoeba histolytica, complement membrane attack complex inhibition by
Protein sequences...
of galactose-specific adhesin of Entamoeba histolytica and CD59 antigen, homol. of
Adhesion,bio-...
to complement membrane attack complex, by Entamoeba histolytica, galactose-specific adhesin in
CAS REGISTRY NUMBERS:
59-23-4 biological studies, adhesin specific for, of Entamoeba histolytica, complement membrane attack complex inhibition by
80295-58-5 80295-59-6 galactose-specific adhesin of Entamoeba histolytica binding to
82986-89-8 inhibition of, by galactose-specific adhesin of Entamoeba histolytica

3/7/16 (Item 16 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117088287 CA: 117(9)88287s JOURNAL
The human complement regulatory protein CD59 binds to the .alpha.-chain of C8 and to the "b" domain of C9
AUTHOR(S): Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1992 VOLUME: 267 NUMBER: 19 PAGES: 13675-80 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 binding domain complement C 8, antigen CD59 assocn complement C 9
DESCRIPTORS:
Antigens,CD59...
binding to complement C8 .alpha.-chain and complement C9b by, of humans
Molecular association...
of CD59 antigen with human complement C8 .alpha.-chain or C9b
CAS REGISTRY NUMBERS:
80295-58-5 CD59 antigen binding to .alpha.-chain of human

80295-59-6 CD59 antigen binding to b domain of human
83534-36-5 CD59 antigen binding to human

3/7/17 (Item 17 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

117088212 CA: 117(9)88212p JOURNAL
Overlapping but nonidentical binding sites on CD2 for CD58 and a second ligand CD59
AUTHOR(S): Hahn, William C.; Menu, Elisabeth; Bothwell, Alfred L. M.; Sims, Peter J.; Bierer, Barbara E.
LOCATION: Div. Pediatr. Oncol., Dana-Farber Cancer Inst., Boston, MA, 02115, USA
JOURNAL: Science (Washington, D. C., 1883-) DATE: 1992 VOLUME: 256 NUMBER: 5065 PAGES: 1805-7 CODEN: SCIEAS ISSN: 0036-8075 LANGUAGE: English
SECTION:
CA215002 Immunochemistry
IDENTIFIERS: CD2 antigen assocn CD58 CD59
DESCRIPTORS:
Antigens,CD59...
CD2 antigen of humans binding site for, CD58 antigen binding site overlap with
Antigens,CD58...
CD2 antigen of humans binding site for, CD59 antigen binding site overlap with
Adhesion,bio-...
CD2 antigen of humans mediation of, CD58 and CD59 as ligands in, overlapping binding sites in relation to
Antigens,CD2...
CD58 and CD59 antigens assocn. with human, overlapping binding sites in
Lymphocyte,T-cell...
CD58 and CD59 overlapping binding sites for human CD2 antigen on
Molecular association...
of CD58 and CD59 with human CD2 antigen, overlapping binding sites in

3/7/18 (Item 18 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

116253695 CA: 116(25)253695n JOURNAL
Contribution of the N-linked carbohydrate of erythrocyte antigen CD59 to its complement-inhibitory activity
AUTHOR(S): Ninomiya, Haruhiko; Stewart, Betty H.; Rollins, Scott A.; Zhao, Ji; Bothwell, Alfred L. M.; Sims, Peter J.
LOCATION: Health Sci. Cent., Univ. Oklahoma, Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1992 VOLUME: 267 NUMBER: 12 PAGES: 8404-10 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA215002 Immunochemistry
IDENTIFIERS: CD59 antigen carbohydrate/complement inhibition

3/7/19 (Item 19 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

115133684 CA: 115(13)133684r JOURNAL
Inhibition of homologous complement by CD59 is mediated by a species-selective recognition conferred through binding to C8 within C5b-8 or C9 within C5b-9

AUTHOR(S): Rollins, Scott A.; Zhao, Ji; Ninomiya, Haruhiko; Sims, Peter J.
LOCATION: Cardiova[redacted] Biol. Res. Program, Oklahoma . Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1991 VOLUME: 146 NUMBER: 7 PAGES: 2345-51
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: CD59 antigen homologous complement inhibition, C9 CD59 antigen homologous complement inhibition
DESCRIPTORS:
Hemolysis...
complement-mediated, CD59 antigen inhibition of homologous, species selectivity of, binding to complement C8 and C9 in
Antigens,CD59...
homologous complement inhibition by, species selectivity of, binding to complement C8 and C9 in
Complement...
inhibition of homologous, by CD59 antigen, species selectivity of, binding to complement C8 and C9 in
CAS REGISTRY NUMBERS:
82986-89-8 CD59 antigen binding to complement C8 and C9 of, in species-selective homologous complement inhibition
80295-58-5 80295-59-6 CD59 antigen binding to, of C5b-9 complex, in species-selective homologous complement inhibition

3/7/20 (Item 20 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

115129040 CA: 115(13)129040k JOURNAL
Amplified gene expression in CD59-transfected Chinese hamster ovary cells confers protection against the membrane attack complex of human complement
AUTHOR(S): Zhao, Ji; Rollins, Scott A.; Maher, Stephen E.; Bothwell, Alfred L. M.; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, 73104, USA
JOURNAL: J. Biol. Chem. DATE: 1991 VOLUME: 266 NUMBER: 20 PAGES: 13418-22 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA203004 Biochemical Genetics
CA213XXX Mammalian Biochemistry
CA215XXX Immunochemistry
IDENTIFIERS: human CD59 antigen CHO cell surface, antigen CD59 CHO cell protection complement, transfection CHO cell human CD59 cDNA
DESCRIPTORS:
Gene and Genetic element,animal...
for antigen CD59, of human, transfection of CHO cells with, surface expression and protection against human complement conferred by
Animal cell line,CHO...
human CD59 antigen surface expression on transfected, protection against human complement conferred by
Transformation,genetic...
of CHO cells, with human antigen CD59 cDNA, surface expression and protection against human complement subsequent to
Antigens,CD59...
surface expression on transfected CHO cells of human, protection against human complement conferred by
CAS REGISTRY NUMBERS:
80295-55-2 80295-56-3 80295-57-4 80295-58-5 80295-59-6 of human, surface expression of human antigen CD59 on transfected CHO cells conferring protection against

3/7/21 (Item 21 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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114099628 CA: 114(11)99628t JOURNAL
Regulatory control of the terminal complement proteins at the surface of human endothelial cells: neutralization of a C5b-9 inhibitor by antibody to CD59
AUTHOR(S): Hamilton, Karen K.; Ji, Zhao; Rollins, Scott; Stewart, Betty H.; Sims, Peter J.
LOCATION: Cardiovasc. Biol. Res. Program, Oklahoma Med. Res. Found., Oklahoma City, OK, USA
JOURNAL: Blood DATE: 1990 VOLUME: 76 NUMBER: 12 PAGES: 2572-7
CODEN: BLOOAW ISSN: 0006-4971 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement regulation CD59 antigen endothelium, blood vessel CD59 antigen complement
DESCRIPTORS:
Complement...
activation of, CD59 antigen regulation of human endothelial cell response to
Antigens,CD59...
complement terminal protein-mediated activation of human endothelial cell regulation by
Blood vessel,endothelium,metabolism...
complement terminal proteins activation of human, CD59 antigen regulation of
CAS REGISTRY NUMBERS:
82986-89-8 endothelial cell of humans activation by, CD59 antigen regulation of

3/7/22 (Item 22 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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113057087 CA: 113(7)57087q JOURNAL
The complement-inhibitory activity of CD59 resides in its capacity to block incorporation of C9 into membrane C5b-9
AUTHOR(S): Rollins, Scott A.; Sims, Peter J.
LOCATION: Health Sci. Cent., Oklahoma Univ., Oklahoma City, OK, 73104, USA
JOURNAL: J. Immunol. DATE: 1990 VOLUME: 144 NUMBER: 9 PAGES: 3478-83
CODEN: JOIMA3 ISSN: 0022-1767 LANGUAGE: English
SECTION:
CA215004 Immunochemistry
IDENTIFIERS: complement C9 inhibition CD59 antigen
DESCRIPTORS:
Complement...
activation of, CD59 antigen inhibition of, mechanism of human
Glycophospholipids,phosphatidylinositol-contg....
as membrane anchor for CD59 antigen
Marchiafava-Micheli syndrome...
CD59 antigen expression on erythrocytes of humans with
Cell membrane...
CD59 antigen of erythrocyte, complement-mediated lysis inhibition by, mechanism of human
Antigens,CD59...
complement inhibition by, mechanism of human
Hemolysis...
complement-mediated, CD59 antigen inhibition of, mechanism of human
CAS REGISTRY NUMBERS:
82903-91-1 assembly of, antigen CD59 inhibition of complement C9 incorporation in, of human

80295-58-5 binding of, to membrane-bound C5b-67, CD59 antigen effect on, of human
101754-00-1 complem[redacted] C8 binding to membrane bound[redacted]59 antigen effect on, of human
82986-89-8 complement C9 incorporation into membrane-assocd., antigen CD59 inhibition of human
80295-59-6 polymn. of and incorporation into membrane complex C5b-9 of, antigen CD59 inhibition of, of human

```
>>>Unmatched parentheses
? s (c9)(20n)(359 or 384)

>>>Operator "(9C)" in invalid position
? s (c9)(20n)(359 or 384)

>>>Operator "(9C)" in invalid position
? s c9 and (359 or 384)

            4106  C9
            2644  359
            3327  384
      S5      11  C9 AND (359 OR 384)
? rd s5

...completed examining records
      S6       5  RD S5 (unique items)
? t s6/7/all


 6/7/1     (Item 1 from file: 55)
DIALOG(R)File  55:Biosis Preiviews(R)
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10316377   BIOSIS NO.: 199698771295
Role of a disulfide-bonded peptide loop within human complement C9 in
  the species-selectivity of complement inhibitor CD59.

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JOURNAL: Biochemistry  35 (10):p3263-3269 1996
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: the C5b-9 membrane attack complex (MAC), thereby protecting human
  cells from lysis by human complement. The complement-inhibitory activity
  of CD59 is species-selective, and is most effective toward C9
  derived from human or other primate plasma. The species-selective
  activity of CD59 was recently used to map the segment of human C9
  that is recognized by this MAC inhibitor, using recombinant rabbit/human
  C9 chimeras that retain lytic function within the MAC (Husler, T.,
  Lockert, D. H., Kaufman, K. M., Sodetz, J. M., & Sims, P. J. (1995) J.
  Biol. Chem. 270,3483-3486). These experiments suggested that the CD59
  recognition domain was contained between residues 334 and 415 in human
  C9. By analyzing the species-selective lytic activity of
  recombinant C9 with chimeric substitutions internal to this
  segment, we now demonstrate that the site in human C9 uniquely
  recognized by CD59 is centered on those residues contained between
  C9 Cys359/Cys384, with an additional contribution by residues
  C-terminal to this segment. Consistent with its role as a CD59
  recognition domain, CD59 specifically bound a human C9-derived
  peptide corresponding to residues 359-384, and antibody (Fab)
  raised against this C9-derived peptide inhibited the lytic activity
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of human MAC. Mutant human **C9** in which Ala was substituted for Cys359/**384** was found to express normal lytic activity and to be fully inhibited by CD59. This suggests that the intrachain Cys359/Cys384 disulfide bond within **C9** is not required to maintain the conformation of this segment of **C9** for interaction with CD59.

6/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

10241203 BIOSIS NO.: 199698696121
Identification of disulfide bonds in the ninth component (**C9**) of human complement.

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JOURNAL: FEBS Letters 380 (1-2):p8-12 1996
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: **C9** is the most abundant protein of the membrane attack complex of complement. By means of limited proteolysis, different chromatographic techniques, a thiol-specific fluorescence assay, amino acid analysis, and Edman degradation, 9 out of 12 disulfide bridges are definitely assigned (Cys-22-Cys-57, Cys-33-Cys-36, Cys-67-Cys-73, Cys-121-Cys-160, Cys-233-Cys-234, Cys-**359**- Cys-**384**, Cys-489-Cys-505, Cys-492-Cys-507, Cys-509-Cys-518). Weaker evidence permits to reduce the number of possible configurations for the remaining 3 cystines (Cys-80-Cys-91, Cys-86-Cys-104, Cys-98-Cys-113, or Cys-80-Cys-91, Cys-86-Cys-113, Cys-98-Cys-1014). These findings are discussed in comparison with the strongly related components C6, C7, C8-alpha, and C8-beta.

6/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

09594903 BIOSIS NO.: 199598049821
The functions of the ninth component of human complement are sustained by disulfide bonds with different susceptibilities to reduction.

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JOURNAL: Biochimica et Biophysica Acta 1209 (1):p117-122 1994
ISSN: 0006-3002
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purified **C9** with expected hemolytic and polymerizing activities was found to contain apprxeq 0.2 mol of sulfhydryl groups/mol of **C9**. By proteolysis of **C9** with labeled SH groups, the SH residues on intact **C9** were mapped to Cys-**359** and Cys-**384** which, presumably, form an intra-domain disulfide bond in the intact molecule. The blocking of these sulfhydryl residues by alkylation, however, had minimal influence on the functions of **C9**. On the other hand, reduction of **C9** by 1 mM dithiothreitol (DTT) (6-fold molar

excess over Cys residues) followed by alkylation resulted in a complete block of polymeriz[redacted]on activity and a 50% loss of [redacted] hemolytic activity. In contr[redacted], the ability of **C9** to bind E[redacted]8 remained largely unaffected. The loss of poly-**C9** formation activity correlated with the alkylation of approx. 6 liberated sulfhydryl groups. Hemolytic activity was abolished by treatment with gt 5 mM DTT which allowed the liberation of apprxeq 18 sulfhydryl groups. Most of the DTT-susceptible disulfides were within the C9a fragment (an N-terminal peptide derived by thrombin). Thus, three major functions of **C9**, EAC1-8 binding, polymerization, and hemolytic activity, are sustained by disulfide bond-dependent conformational motifs with different susceptibility to reducing reagents. The maintenance of the N-terminal C9a region is essential for polymerization, but not EAC1-8 binding activity of **C9**. Taken together, the results of the present study differentiate in molecular terms several of the functional portions of **C9**, and stress the significance of intra-chain disulfide linkages in maintaining the structural components necessary for the functions of **C9**.

6/7/4 (Item 4 from file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

09545784 BIOSIS NO.: 199598000702
Identity of a Peptide Domain of Human **C9** That Is Bound by the Cell-surface Complement Inhibitor, CD59.

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JOURNAL: Journal of Biological Chemistry, 269 (42):p26424-26430 1994
ISSN: 0021-9258
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The CD59 antigen is a plasma membrane glycoprotein that serves as an inhibitor of the C5b-9 complex of complement. This inhibitory activity appears related to the capacity of CD59 to bind with high affinity to sites that are nascently exposed in the alpha-chain of human C8, as well as within the C9b domain (amino acid residues 245-538) of human **C9**, during assembly of the C5b-9 complex on the target membrane (Ninomiya, H., and Sims, P. J. (1992) J. Biol. Chem. 267, 13675-13680). The CD59 binding site in **C9** was first investigated by N-terminal sequencing of CD59-binding peptides generated by limited digest of the isolated C9b domain. These experiments revealed a 17-kDa fragment (starting at **C9** residue Thr-320) that retained affinity for CD59, suggesting the possibility for localizing the CD59 binding site by mapping with small **C9**-derived peptides. Peptides spanning the entire C9b sequence were expressed in Escherichia coli and then probed with CD59. CD59 bound specifically to all peptides starting N-terminal to **C9** residue **359** with C termini extending beyond residue 411. Little to no CD59 binding was observed for various **C9**-derived peptides that started C-terminal to residue **359** or that were truncated N-terminal to residue 411. Affinity-purified antibody against **C9** residues 320-411 inhibited CD59 binding to **C9** by gt 50% and completely inhibited its binding to the isolated C9b domain. Little to no specific binding of CD59 was detected for peptides restricted to the putative hinge domain within Cgb (residues 245-271). These results indicate that a CD59 binding site is located between residues 320 and 411 of the **C9** polypeptide and suggest that the affinity of this site is principally determined by residues **359**-411.

6/7/5 (Item 5 f[redacted] file: 55)
DIALOG(R)File 55:Biosis Preiviews(R)

09124505 BIOSIS NO.: 199497132875
A structural model of the tetrodotoxin and saxitoxin binding site of the Na+ channel.

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JOURNAL: Biophysical Journal 66 (1):p1-13 1994
ISSN: 0006-3495
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Biophysical evidence has placed the binding site for the naturally occurring marine toxins tetrodotoxin (TTX) and saxitoxin (STX) in the external mouth of the Na+ channel ion permeation pathway. We developed a molecular model of the binding pocket for TTX and STX, composed of antiparallel beta-hairpins formed from peptide segments of the four S5-S6 loops of the voltage-gated Na+ channel. For TTX the guanidinium moiety formed salt bridges with three carboxyls, while two toxin hydroxyls (**C9**-OH and C10-OH) interacted with a fourth carboxyl on repeats I and II. This alignment also resulted in a hydrophobic interaction with an aromatic ring of phenylalanine or tyrosine residues for the brain II and skeletal Na+ channel isoforms, but not with the cysteine found in the cardiac isoform. In comparison to TTX, there was an additional interaction site for STX through its second guanidinium group with a carboxyl on repeat IV. This model satisfactorily reproduced the effects of mutations in the S5-S6 regions and the differences in affinity by various toxin analogs. However, this model differed in important ways from previously published models for the outer vestibule and the selectivity region of the Na+ channel pore. Removal of the toxins from the pocket formed by the four beta-hairpins revealed a structure resembling a funnel that terminated in a narrowed region suitable as a candidate for the selectivity filter of the channel. This region contained two carboxyls (Asp-**384** and Glu-942) that substituted for molecules of water from the hydrated Na+ ion. Simulation of mutations in this region that have produced Ca-2+ permeation of the Na+ channel created a site with three carboxyls (Asp-**384**, Glu-942, and Glu-1714) in proximity.